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NEWER DISEASE-TARGETED AGENTS FOR SICKLE CELL DISEASE

L-glutamine (Endari)
Voxelotor (Oxbryta)
Crizanlizumab (Adakveo)

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ABBREVIATIONS

β	Beta
ACS	Acute chest syndrome
AEs	Adverse events
ASH	American Society of Hematology
ATS	American Thoracic Society
AUC	Area under the curve
CDC	Centers for Disease Control and Prevention
CGI-C	Clinical Global Impression of Change
CI	Confidence interval
CKD	Chronic kidney disease
CYP	Cytochrome
DUR	Drug Utilization Review
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
Hb	Hemoglobin
HbC	Hemoglobin C
HbF	Fetal hemoglobin
HbS	Hemoglobin S; Sickle hemoglobin
HPLC	High performance liquid chromatography
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplantation
IgG	Immunoglobulin G
ITT	Intention-to-treat
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NAD	Nicotinamide adenine
NBS	Newborn screening
NHLBI	National Heart, Lung, and Blood Institute
NSAIDs	Nonsteroidal anti-inflammatory drugs
PA	Prior authorization
PSGL-1	P-selectin glycoprotein ligand 1
RCTs	Randomized controlled trials
SAEs	Serious adverse events
SCA	Sickle cell anemia
SCD	Sickle cell disease
SCDC	Sickle cell data collection
SCT	Sickle cell trait
TCD	Transcranial Doppler ultrasound
US	United States
VOC	Vaso-occlusive crises

1.0 INTRODUCTION

Sickle cell disease (SCD) is a rare, chronic, hereditary hematological disorder caused by a mutation in the beta (β)-globin subunit of the hemoglobin (Hb) gene.[1-4] It is inherited in an autosomal recessive pattern. This mutation negatively impacts the oxygen carrying capacity and functioning of erythrocytes.[1-4] Individuals with SCD have abnormal Hb (known as sickle hemoglobin [HbS]),[5,6] resulting in erythrocytes with a rigid, adhesive, and sickle-shaped morphology.[1,2] The sickling phenomenon leads to premature hemolysis, chronic anemia, and eventual multi-organ damage.[1,2,7] Sickled erythrocytes tend to adhere and obstruct microvasculature capillaries,[3] causing vaso-occlusive events (eg, stroke, acute chest syndrome [ACS], venous thromboembolism), and other complications (eg, pain crises, kidney dysfunction) that often worsen with age.[1,2,5,7]

SCD comprises of several genetic hemoglobinopathies that are distinguished by alterations in the β-globin alleles.[8,9] The 3 most prevalent genotypes of SCD are HbSS, HbSC, and HbSβ-thalassemia.[1] Typically, HbSS and HbSβ^0-thalassemia denote a severe disease manifestation, whereas the HbSC genotype is associated with milder severity.[1]

Currently, there are 4 disease-modifying agents approved by the United States (US) Food and Drug Administration (FDA) for the treatment of SCD, all with distinct mechanisms of action and labeled indications.[1]

1. Hydroxyurea (Droxia, 1998) was the first of these agents to gain approval for the treatment of SCD, and is indicated to decrease the frequency of painful crises and the requirement for blood transfusions in patients with **sickle cell anemia** (SCA) who experience recurrent moderate to severe painful crises.[10] A subsequent brand of hydroxyurea (Siklos, 2017) was later approved for the same indication but in children aged ≥2 years.[1,11-13]
2. In 2017, L-glutamine (Endari) was approved to decrease acute complications of SCD in patients ≥5 years of age.[14]
3. More recently in 2019, the FDA approved voxelotor (Oxbryta).[15] Voxelotor has a general indication for the treatment of SCD in patients ≥4 years of age; this indication was extended from the initial approved age of ≥12 years following an accelerated approval.[15,16]
4. The first monoclonal antibody for SCD, crizanlizumab (Adakveo), was approved in 2019.[17] Crizanlizumab is indicated to decrease the occurrence of vaso-occlusive crises (VOC) in patients aged ≥16 years with SCD.[17]

All of these agents approved for this rare disorder are designated as orphan drugs.[18-22] Three of the agents are orally administered on a daily basis, and the fourth, crizanlizumab, is intravenously administered every 4 weeks.[10,13-15,17] **Table 1** summarizes the FDA approved indication, available formulations, and mechanism of action for each agent.

The objective of this report is to provide evidence on the safety and efficacy of the latest disease-modifying therapies (L-glutamine, voxelotor, and crizanlizumab) for SCD, and to recognize potential barriers to care regarding the accessibility of these newer agents. This report addresses recent US guideline recommendations for the pharmacologic management of SCD, efficacy and safety evidence from pivotal randomized controlled trials (RCTs), safety information from product labeling, and

published literature on patient/provider perspectives on barriers to accessing reviewed pharmacologic agents. Upcoming reports will address other barriers to care to help inform recommendations related to Utah House Bill 487.[23]

Table 1. FDA-Approved Indication and Mechanism of Action for Disease-targeted Agents for Sickle Cell Disease

Generic name Brand name (approval year)	FDA-approved labeled indication	Indicated population for use	Mechanism of action (MOA)	Route of administration	Maintenance dosing frequency
Hydroxyurea (Droxia, 1998; Siklos, 2017)[5,10,12,13] • Droxia: capsule • Siklos: tablet	To decrease the frequency of painful crises and the requirement for blood transfusions among patients with **sickle cell anemia** who suffer from recurring moderate to severe painful crises	• Droxia: unspecified age for use • Siklos: pediatric (**aged ≥2 years**) and adult patients with SCD	• Exact MOA remains unknown • Known beneficial effects include: ○ increase HbF concentrations ○ decreases neutrophils ○ reduces adhesion of erythrocytes to vasculature endothelium	Oral	Once daily
L-glutamine (Endari, 2017)[14] • Powder	To decrease the acute complications of SCD	Pediatric (**aged ≥5 years**) and adult patients with SCD	Increases the amount of reduced glutathione in sickled erythrocytes, thereby reestablishing the NAD redox equilibrium	Oral	Twice daily
Voxelotor (Oxbryta, 2019)[15] • Tablet, including for oral suspension	Treatment of SCD	Pediatric (**aged ≥4 years**) and adult patients with SCD	HbS polymerization inhibitor by stabilizing Hb in the oxygenated state	Oral	Once daily
Crizanlizumab (Adakveo, 2019)[17] • Solution for intravenous use	To decrease the frequency of vaso-occlusive crises	Pediatric (**aged ≥16 years**) and adult patients with SCD	A humanized IgG_2 kappa monoclonal antibody that blocks P-selectin from interacting with PSGL-1	Intravenous infusion	Every 4 weeks

Abbreviations: FDA, US Food and Drug Administration; Hb, hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin or hemoglobin S; IgG, immunoglobulin G; MOA, mechanism of action; NAD, nicotinamide adenine dinucleotide; PSGL-1, P-selectin glycoprotein ligand 1; SCD, sickle cell disease

2.0 METHODS

We queried two bibliographic databases (Ovid Medline and Embase), using controlled vocabulary and free-text terms, for RCTs addressing the efficacy and safety of L-glutamine, voxelotor, or crizanlizumab. RCTs were identified in both databases using a Cochrane Collaboration Handbook filter.[24] The Embase RCT search excluded conference abstracts and was limited to English. We performed supplemental searches in Ovid MEDLINE and Embase to identify newer information for combination use of L-glutamine, voxelotor, or crizanlizumab, with a date restriction of 2022 to current based on a prior systematic review.[25] See **Appendix A** for details on the search strategies.

The prescribing information for each agent, including product labeling and package inserts, was acquired from the website of the respective drug sponsor.

To identify key US guidelines addressing the management of SCD using disease-targeted pharmacotherapies, we searched the following websites:

- UpToDate (referring to guidelines listed under the topic of "sickle cell disease and thalassemias"): https://www.uptodate.com/
- Guideline Central: https://www.guidelinecentral.com/guidelines/
- American Society of Hematology (ASH): https://www.hematology.org/
- American Thoracic Society (ATS): https://www.thoracic.org/
- National Heart, Lung, and Blood Institute (NHLBI): https://www.nhlbi.nih.gov/

3.0 SICKLE CELL DISEASE (SCD) OVERVIEW

Sickle cell disease (SCD) is a rare, chronic, hereditary hematological disorder, inherited in an autosomal recessive pattern,[3] that is the result of a single amino acid substitution in the beta (β)-globin subunit of the hemoglobin (Hb) gene.[3,8,9,16] As a result of the gene mutation,[3,9] individuals with SCD exhibit abnormal Hb (known as sickle hemoglobin [HbS]),[5,6] causing erythrocytes to be rigid, adhesive, and have a sickle-shaped morphology,[1,2,5,9] negatively impacting cell functionality.[9] When subjected to Hb deoxygenation, sickle cells are more likely to polymerize, vaso-occlude, and prematurely hemolyze, driving the underlying pathophysiologic mechanisms of the clinical manifestations of SCD.[4,26] Therefore, the disease is characterized by acute (eg, stroke, priapism, acute chest syndrome [ACS], vaso-occlusive crises [VOC])[27] and chronic complications (eg, chronic pain, pulmonary hypertension, cardiovascular disease, osteoporosis, chronic kidney injury) that affect the majority of organ systems, and tend to worsen with age (see **Table 2**).[5,26] Simultaneous impairment of numerous organ systems can result in multi-organ failure, a severe and life-threatening complication of SCD.[28] Acute pain episodes or VOCs (also commonly called sickle cell pain crises or acute pain crises), are highly prevalent clinical manifestations of SCD, attributed to 95% of SCD-related hospitalizations.[26,29] The frequency of VOCs, in conjunction with ACS is the most prevalent prognosticator of SCD-related mortality.[29] Nonetheless, a high degree of inter-patient variability exists in the clinical manifestations of SCD.[6,9] Even with treatment advances, individuals with SCD continue to have a reduced life expectancy (estimated average: 54 years) of approximately 20 years less than the average lifespan for the general population.[4,30] **Table 2** summarizes some of the common complications of SCD,[1,2,6] which can manifest as early as 5 months of age in affected individuals once fetal Hb (HbF) is depleted.[1,16,31]

Table 2. Common Complications of Sickle Cell Disease[6,16,28 a]

Complication or clinical manifestation	Chronicity (examples, if applicable)[6]		Pathophysiology	Signs/symptoms
	Acute	Chronic		
ACS	✓	--	• Impediment of pulmonary blood perfusion • Potentially due to bacterial or viral infection • Life-threatening emergency	• Coughing • Dyspnea • Tachypnea • Fever • Chest pain • New-onset hypoxia
Anemia	✓ • Aplastic crisis	✓ • Compensated hemolytic anemia	• Premature hemolysis of erythrocytes	• Fatigue • Dizziness • Jaundice • Pale skin color • Difficulty breathing
Avascular Necrosis	--	✓	• Reduced blood perfusion to the bone tissue	• Mild to severe join pain • Patients can be asymptomatic
Dactylitis	✓	--	• Impediment of blood perfusion to the bones in the distal limbs (ie, hands and feet) • Often the first symptom in infants and young children	• Swelling in hands and feet • Fever
Hepatobiliary issues	✓ • Acute intrahepatic cholestasis • Acute sickle hepatic crisis	✓ • Pigment gallstones	• Occlusion of blood flow to the liver • Premature hemolysis of erythrocytes leading to excess bilirubin	• Upper right quadrant abdominal pain • Jaundice • Nausea • Vomiting
Infection	✓ • Pneumonia • Meningitis	✓ • Leg ulcers • Osteomyelitis	• Reduced tissue perfusion • Functional hyposplenism or asplenism • Altered cellular and/or humoral immunity	• Symptoms vary by type of infection • Fever
Kidney issues	✓ • Acute kidney injury • Acute nephrotic syndrome	✓ • Chronic kidney failure • Concentrating defect	• Reduced blood perfusion to the kidney due to the crescent-shape morphology of the erythrocytes	• Hypertension • Polyuria • Fatigue • Shortness of breath • Hematuria • Nocturnal enuresis
Leg Ulcers	--	✓	• Reduced blood perfusion to the legs	• Open sores • Swelling • Localized pain • Pruritus

Abbreviations: ACS, acute chest syndrome; DVT, deep vein thrombosis; PE, pulmonary embolism; VOE, vaso-occlusive episode; VTE, venous thromboembolism

Table 2. Common Complications of Sickle Cell Disease[6,16,28 a]

Complication or clinical manifestation	Chronicity (examples, if applicable)[6]		Pathophysiology	Signs/symptoms
	Acute	Chronic		
Ocular issues	✓ • Retinal detachment • Retinal artery occlusion	✓ • Proliferative retinopathy • Permanent vision loss	• Vaso-occlusion of the ocular vasculature, most commonly in the retina	• Visual disturbances
Pain	✓ • Acute VOE • ACS	✓ • Pain from osteonecrosis, ulcers, or tissue infarction	• Adhesion and obstruction of microvasculature capillaries	• Pain is usually localized to the extremities (hands, feet), chest, or back • Chronic pain is defined as pain lasting >6 months
Priapism (ischemic)	✓	--	• Crescent-shape morphology of the erythrocytes can cause a prolonged erection (>2 hours) in males • Repeated episodes can cause erectile dysfunction	• Painful and rigid penis • Swelling • Difficulty urinating
Pulmonary hypertension	--	✓	• Changes to the pulmonary arterial vasculature via chronic hemolysis of erythrocytes[32] • Chronic inflammation and endothelial injury contribute to vascular remodeling[32]	• Chest pain or discomfort • Swelling of the legs, ankles, or abdomen • Fatigue • Difficulty breathing • Dizziness
Sleep disordered breathing syndromes, including sleep apnea	--	✓	• Nocturnal hypoxemia results from the decreased oxygen-carrying capacity of erythrocytes and hemolysis, and other multifactorial reasons	• Excessive tiredness when awake • Struggle for air when asleep • Episodes of not breathing while asleep • Irritability • Loud snoring
Splenic sequestration crisis	✓	--	• Splenic enlargement as a consequence of sickled erythrocytes becoming trapped in the spleen	• Pain on the left side of the abdomen • May result in anemia if untreated • Sudden weakness • Tachypnea • Tachycardia • Dyspnea

Abbreviations: ACS, acute chest syndrome; DVT, deep vein thrombosis; PE, pulmonary embolism; VOE, vaso-occlusive episode; VTE, venous thromboembolism

Table 2. Common Complications of Sickle Cell Disease[6,16,28] [a]

Complication or clinical manifestation	Chronicity (examples, if applicable)[6]		Pathophysiology	Signs/symptoms
	Acute	Chronic		
Stroke (ischemic, hemorrhagic)	✓	--	• Vaso-occlusion of the cerebral vasculature[33]	• Hemiparesis or hemiplegia • Acute aphasia or dysarthria • Visual disturbance in one or both eyes • Acute ataxia • Intense, sudden headache with no known etiology
VTE (DVT, PE)	✓	--	• Crescent-shape morphology of the erythrocytes	DVT: • Swelling • Erythema • Pain • Tenderness PE: • Difficulty breathing • Hypotension • Chest pain • Cough

Abbreviations: ACS, acute chest syndrome; DVT, deep vein thrombosis; PE, pulmonary embolism; VOE, vaso-occlusive episode; VTE, venous thromboembolism

3.1 Genotypes of SCD

SCD comprises of several genetic hemoglobinopathies that result from the inheritance of two abnormal β-globin alleles: either two copies of HbS (ie, mutated alleles of Hb) or one copy of HbS with another abnormal gene variant (eg, hemoglobin C [HbC]).[1,9,27,34] The genotype of SCD depends on the inherited hemoglobinopathy, which plays a role in SCD severity.[1] In general, patients with sickle cell anemia (SCA; typically defined as genotypes HbSS or HbSβ^0-thalassemia)[16,35] tend to have greater disease severity than those with other genotypes of SCD (eg, HbSβ$^+$-thalassemia, HbSC).[8,26,27,36] The most common genotypes of SCD are HbSS (60%−65%), HbSC (25%−30%), and HbSβ-thalassemia (5%−10%).[1,16] There are also rare variants of SCD that include HbSE, HbSD, and HbSO, which range in disease severity.[1]

Although not typically a symptomatic genotype,[1,5,27,37] sickle cell trait (SCT) occurs in heterozygous carriers of a normal Hb allele (HbA) and a HbS allele.[1,5,27,37] In rare cases, SCT carriers may experience complications (eg, pain crises),[37] especially under conditions that stress the body (eg, intense exercise, dehydration).[1] Additionally, SCT individuals can pass the HbS gene to their offspring.[1,2,37]

3.2 Incidence of SCD

Although the exact number of SCD cases in the US is unknown, the current best estimate suggests there are approximately 100,000 Americans with SCD[38]; these individuals are predominately of Hispanic (1 in 36,000 births) or African American (1 in 365 births) descent.[4,16] The prevalence of SCT in the US is 15.5 cases per 1,000 neonates.[16] Globally, the incidence of SCD and SCT varies significantly based on geographic location, with the highest rates observed in populations originating from sub-Saharan Africa, Central America, Caribbean, Saudi Arabia, India, and Mediterranean countries.[3,16,26,38] Annually, about 300,000 to 400,000 newborns are diagnosed with SCD worldwide.[4,26,31]

3.3 Sickle Cell Data Collection (SCDC) Program

The Sickle Cell Data Collection (SCDC) Program, managed by the Centers for Disease Control and Prevention (CDC), gathers comprehensive health data on individuals affected by SCD to analyze long-term treatment, diagnostic, and accessibility patterns for those living with the disease in the US.[39] Currently, there are 12 states with newborn screening (NBS), and/or demographic and healthcare utilization data available on the CDC website, but Utah is not one of them.[40,41]

4.0 DIAGNOSIS OF SCD

SCD, including SCT, is diagnosed using a blood test, more specifically a complete blood count with mean corpuscular volume, **and** Hb electrophoresis, high performance liquid chromatography (HPLC), or genetic testing, among other tests (eg, isoelectric focusing, polymerase chain reaction-based techniques).[31,36,42] Hb electrophoresis, isoelectric focusing, and HPLC are able to detect Hb variants (eg, HbC, HbS).[36] Note that diagnostic tests may have limitations regarding which Hb variants they can identify.[36]

Since 2006, the screening of SCD has been a part of routine NBS,[1,42] and has universally been conducted across all 50 states,[16,42] including Utah.[43] Therefore, for children born in the US, SCD is most commonly detected shortly after birth[1]; screening for sickle cell status should occur 24−48 hours after delivery.[42] To

confirm the diagnosis in infants with a positive result, re-testing within 2 months can be considered,[16,35] and may be necessary in cases of uncertainity.[44] SCD can also be diagnosed during prenatal stages using pre-birth diagnostic procedures such as chorionic villus sampling or amniocentesis to assess chromosomal or genetic irregularities in the fetus.[1,44] Although NBS is routinely conducted, some neonates with SCD may remain undetected due to the following factors[16]:

- Extreme prematurity
- Previous blood transfusion
- Challenges in contacting their family
- Immigration from counties that lack routine NBS

Screening for SCD and SCT may also be performed in adulthood, particularly for those who want to become or are currently pregnant, or postpartum.[35,42]

5.0 PHARMACOTHERAPEUTIC TREATMENT OF SCD

The treatment goal of SCD is to minimize hospitalizations, mitigate complications, reduce mortality, and enhance the patient's overall quality of life.[16] Available disease-targeting pharmacotherapies (ie, hydroxyurea, L-glutamine, voxelotor, crizanlizumab) are not curative. The only FDA-approved curative treatment for SCD is hematopoietic stem cell transplantation (HSCT),[27,34,45] but this procedure can have serious complications (eg, graft-versus-host disease, sepsis, seizures).[1,16] There are also several gene therapies currently in-development aimed at curing SCD.[9]

There are 4 disease-modifying agents currently approved by the US Food and Drug Administration (FDA) for the treatment of SCD: hydroxyurea (Droxia, Siklos), L-glutamine (Endari), voxelotor (Oxbryta), and crizanlizumab (Adalveo).[1] All of these agents are designated as orphan drugs for this rare disorder.[3,18-22] Hydroxyurea (Droxia) was the first disease-modifying pharmacotherapy to be approved in 1998, followed by L-glutamine in 2017, and voxelotor and crizanlizumab in 2019.[5,14,15,17,46] Hydroxyurea is a ribonucleotide reductase inhibitor that increases erythrocyte HbF concentrations and water content, decreases neutrophils, and reduces adhesion of erythrocytes to vasculature endothelium.[13,16,27,46] But, the exact mechanism by which it produces these effects remains unknown.[13] Hydroxyurea produces benefits for patients with SCD (eg, reducing the frequency of ACS and VOCs) and potentially increases long-term surivial.[11,27,46] The exact mechanism by which L-glutamine, an amino acid, exerts its therapeutic effects is also not entirely understood, but it may play a role in regulating and preventing oxidative injury that would otherwise lead to hemolysis and vaso-occulsion.[14] It is thought that L-glutamine reestablishes nicotinamide adenine dinucleotide (NAD) redox equilibrium via increasing the amount of reduced glutathione in sickled erythrocytes.[14] Voxelotor inhibits HbS polymerization by reversibly binding to Hb and stabilizing its oxygenated form.[7,15] Crizanlizumab is a humanized immunoglobulin G $(IgG)_2$ kappa monoclonal antibody that blocks P-selectin,[17] an adhesion molecule,[16] from interacting with P-selectin glycoprotein ligand 1 (PSGL-1), thus preventing sickled erythrocytes and other blood cells (ie, platelets, leukocytes) from adhering to the vascular endothelium.[17]

These disease-modifying agents for the treatment of SCD differ in several aspects, including age of approved use, labeled indication, and route and/or frequency of administration. With the exception of Droxia which does not provide a specific age for approved use,[10] all agents are labeled for use in adult and pediatric populations but pediatric ages differ: hydroxyurea (as Siklos) in patients ≥2 years of age,

voxelotor in patients ≥4 years of age, L-glutamine in patients ≥5 years of age, and crizanlizumab in patients ≥16 years of age.[13-15,17] Hydroxyurea is indicated for patients with **SCA**, which experts refer to as HbSS or HbSβ^0-thalassemia genotypes.[10,11,13,35,47] However, the labeled indication does not explicitly name a particular genotype or state whether it is referring to the general clinical manifestation of SCD-related anemia.[10,13] The remaining disease-modifying agents are indicated for SCD.[14,15,17] Furthermore, although each of these agents are approved for the treatment of SCD, the indicated purpose for use (*highlighted in blue text below*) varies among them (see note[*]):

- *To decrease the frequency of painful crises and the requirement for blood transfusions in patients with recurrent moderate to severe painful crises*[10,13]: hydroxyurea (Droxia, Siklos)
- *To reduce sickle cell-related acute complications*[14]: L-glutamine
- *To decrease the frequency of VOCs*[17]: crizanlizumab

All agents are administered orally, except crizanlizumab which is administered by intravenous infusion.[10,13-15,17] Crizanlizumab must be prepared and administered by a healthcare provider in a health care setting.[17] The dosage formulation of the oral agents varies: L-glutamine is available as a powder, voxelotor is available as tablets, including for oral suspension, and hydroxyurea is available as capsules (Droxia), or tablets (Siklos).[10,13-15] Because L-glutamine is an oral powder, it must be mixed into 8 oz of liquid (eg, milk, water, apple juice), at cold or room temperature, or 4−6 oz of soft food (eg, applesauce, yogurt) before consuming.[14] Additionally, voxelotor tablets for oral suspension should be dispersed in a clear liquid at room temperature before drinking.[15] The dosing frequency of crizanlizumab is every 4 weeks after receiving 2 loading doses at Week 0 and Week 2; twice daily for L-glutamine; and once daily for voxelotor and hydroxyurea.[10,13-15,17] All of these agents are intended for long-term use.[11,48]

Table 3 provides an overview of the recommended dosing for reviewed agents; see **Table 1** for a summary of the labeled indications, including approved age of use, and mechanism of action.

[*] Voxelotor has a general indication for the treatment of SCD.[15]

Table 3. FDA-Approved Indication and Dosing Recommendations for Disease-targeted Agents for Sickle Cell Disease

Active ingredient and formulation (Brand)	Dosing and administration recommendations

Hydroxyurea (Droxia; Siklos)[5,10,12,13]
 	
• Droxia: oral capsule
  ○ 200 mg, 300 mg, 400 mg
• Siklos: oral tablet
  ○ Scored: 100 mg
  ○ Triple-scored: 1,000 mg
	• Initial dose:
	  ○ **Adults**: 15 mg/kg by mouth once daily (Droxia and Siklos)
	  ○ **Children**: 20 mg/kg by mouth once daily (Siklos)
	  ▪ Blood counts should be monitored every two weeks
	  ○ Dosages may be escalated by 5 mg/kg/day every 8 weeks[a] (Siklos) or every 12 weeks (Droxia) until the max dose or the highest tolerated dose is achieved
	• Discontinue the agent if blood counts are within a toxic range
	  ○ Resume the agent at a reduced dose by 2.5 mg/kg/day (Droxia) or 5 mg/kg/day (Siklos) from the previous dosage once the patient's hematologic values have recovered
	• Max dose: 35 mg/kg/day
	• Renal impairment: decrease the dose by 50% in patients with a CrCl <60 mL/min

L-glutamine (Endari)[14]
 	
• Oral powder: 5 g per packet
	• Recommended dose:
	  ○ 5 g to 15 g by mouth twice daily, depending on body weight
	  ▪ <30 kg: 5 g (1 packet); total daily dose = 10 g (2 packets daily)
	  ▪ 30 to 65 kg: 10 g (2 packets); total daily dose = 20 g (4 packets daily)
	  ▪ >65 kg: 15 g (3 packets); total daily dose = 30 g (6 packets daily)
	• Dose should be mixed into 8 oz of liquid (eg, milk, water, apple juice), at cold or room temperature, or 4–6 oz of soft food (eg, applesauce, yogurt)

Voxelotor (Oxbryta)[15]
 	
• Oral tablet: 300 mg, 500 mg
• Tablet for oral suspension: 300 mg
	• Recommended dose:
	  ○ ≥12 years of age: 1,500 mg by mouth once daily
	  ○ 4 to <12 years of age: dose based on body weight, by mouth once daily
	  ▪ *10 kg to <20 kg: 600 mg* ▪ *20 kg to <40 kg: 900 mg* ▪ *≥40 kg: 1,500 mg*
	• Severe hepatic impairment (Child Pugh C):
	  ○ ≥12 years of age: 1,000 mg by mouth once daily
	  ○ 4 to <12 years of age: dose based on body weight, by mouth once daily
	  ▪ *10 kg to <20 kg: 300 mg* ▪ *20 kg to <40 kg: 600 mg* ▪ *≥40 kg: 900 mg or 1,000 mg*

[a] *If a severe painful crisis occurs, the dose may be escalated sooner than every 8 weeks[13]*

Abbreviations: CrCl, creatinine clearance; FDA, US Food and Drug Administration; g, gram; IV, intravenous; kg, kilogram; lbs, pounds; mg, milligram; mL, milliliter; SCD, sickle cell disease

Table 3. FDA-Approved Indication and Dosing Recommendations for Disease-targeted Agents for Sickle Cell Disease

Active ingredient and formulation (Brand)	Dosing and administration recommendations
Crizanlizumab (Adakveo)[17] • Single-dose vial: 100 mg/10 mL (10 mg/mL) solution, for IV use	• 5 mg/kg infused IV over 30 minutes at Week 0, Week 2, and then four-week intervals thereafter ○ A healthcare provider should prepare and administer the dose • May be given with or without hydroxyurea

[a] *If a severe painful crisis occurs, the dose may be escalated sooner than every 8 weeks*[13]

Abbreviations: CrCl, creatinine clearance; FDA, US Food and Drug Administration; g, gram; IV, intravenous; kg, kilogram; lbs, pounds; mg, milligram; mL, milliliter; SCD, sickle cell disease

6.0 GUIDELINE TREATMENT RECOMMENDATIONS FOR SCD

Because SCD is a chronic condition that can impact multiple organs, management involves prevention and treatment of pain episodes and other associated complications.[1] Management strategies encompass lifestyle modifications (eg, hand hygiene, avoidance of low-oxygen environments and high altitudes), routine health maintenance including screening (annual eye exams), and targeted pharmacotherapies aimed at averting or treating complications that arise from SCD.[1]

We reviewed 6 US guidelines, published by 3 organizations, that addressed disease-modifying pharmacotherapy (ie, hydroxyurea, L-glutamine, voxelotor, crizanlizumab) for SCD: 1 by the American Thoracic Society (ATS; 2014),[49] 1 by the National Heart, Lung, and Blood Institute (NHLBI; 2014),[35] and 4 by the American Society of Hematology (ASH; 2019–2021).[45,50-52]

To emphasize the intricacy of SCD management, select *preventative measures* were extracted from the 2014 NHLBI guideline, outlined in **Appendix B**.[35] Regarding treatment recommendations, only those pertaining to disease-modifying agents (ie, hydroxyurea, L-glutamine, voxelotor, crizanlizumab) were extracted from reviewed guidelines. For additional guidance on screening, as well as recommendations concerning the utilization of other pharmacologic agents (eg, angiotensin-converting enzyme inhibitors, anticoagulants, opioids), and nonpharmacologic therapies for SCD-associated complications, please refer to the specific guideline(s).

6.1 Disease-targeted pharmacotherapies for the treatment of SCD

The NHLBI and ATS guidelines, both published in 2014, predate FDA approval of the newer disease-targeting pharmacotherapies (ie, L-glutamine, voxelotor, and crizanlizumab) but provide recommendations for the use of hydroxyurea.[35,49] The NHLBI guideline expert panel advised offering hydroxyurea to pediatric patients with SCA, taking into consideration the patients' preferences and values,[35] even though it had yet to gain FDA approval in the pediatric population (no approved medications for pediatric SCD existed at the time in the US).[13] Hydroxyurea was also recommended (and approved) for adults with SCA (which authors defined as HbSS or HbSβ^0-thalassemia) who a) experience ≥3 moderate to severe sickle cell pain crises within a one-year period, b) have sickle cell-associated pain or severe symptomatic chronic anemia that interferes with daily activities and/or quality of life, or c) have a history of recurrent and/or severe ACS.[35] Additionally, the ATS guideline strongly recommended hydroxyurea as first-line treatment in children and adults with SCD and increased mortality risk (defined as those with confirmed pulmonary hypertension by right heart catheterization, a tricuspid regurgitant jet velocity of ≥2.5 m/s, or an N-terminal pro-brain natriuretic peptide of ≥160 pg/mL).[49] Chronic transfusions were suggested as an alternative option.[49] The NHLBI guideline emphasized that hydroxyurea may be beneficial and used for other genotypes of SCD (eg, HbSC) based on physician judgement, especially if the patient's daily activities or quality of life are impacted by recurrent sickle cell-related pain.[35]

The newer SCD guidelines by ASH also does not provide specific recommendations regarding the use of L-glutamine, voxelotor, or crizanlizumab[45,50-52]; however, the most recent ASH guideline from 2021 on stem cell transplantation included L-glutamine and crizanlizumab as part of the standard treatment approach.[45] Other reviewed ASH guidelines primarily addressed the use of hydroxyurea.[50-52]

The 2019 ASH guideline on cardiopulmonary and kidney disease highlighted initiating or optimizing disease-modifying therapies, including hydroxyurea for patients diagnosed with SCD and PAH.[52] In the context of chronic kidney disease (CKD), the use of hydroxyurea may present challenges owing to its suppressive effects on erythropoiesis, particularly when endogenous erythropoietin production is reduced. Consequently, ASH suggests a combination treatment strategy involving erythropoiesis-stimulating agents and hydroxyurea for adults and children with SCD and worsening CKD-related anemia (supported by very low certainty of evidence), instead of using hydroxyurea alone.[52] The 2014 NHLBI guideline shares a similar stance by recommending the addition of hydroxyurea to erythropoietin in adults and children with SCD and comorbid CKD to improve signs or symptoms of anemia.[35]

Although the 2020 ASH guideline on managing acute and chronic pain does not provide specific recommendations for hydroxyurea, L-glutamine, voxelotor, or crizanlizumab, it does acknowledge the efficacy of L-glutamine, crizanlizumab, and hydroxyurea in reducing the incidence of acute pain episodes that require medical treatment among children and adults with SCD.[50] However, some individuals with SCD are intolerant to these medications or may experience residual, persistent, and/or frequent painful episodes despite using these treatments,[50] thereby requiring additive pain treatment (eg, opioids, NSAIDs). Notably, the ASH mentions that in specific clinical scenarios where disease-modifying therapies have demonstrated limited effectiveness in managing recurring pain episodes, a trial of monthly blood transfusions may be considered provided comprehensive shared decision-making can be effectively implemented. Chronic monthly blood transfusions are suggested against as a first-line approach to prevent or alleviate recurrent acute pain episodes.[50]

The 2020 ASH guideline for SCD-related cerebrovascular complications provided recommendations about the use of hydroxyurea for primary and secondary stroke prevention in children with SCD.[51] For primary stroke prevention, the guideline suggested hydroxyurea at the highest tolerated dose as an alternative to regular blood transfusions for children 2−16 years of age with SCD if they have a) abnormal transcranial Doppler ultrasound (TCD) results, b) no silent cerebral infarcts, as measured by magnetic resonance imaging (MRI), or presence of vasculopathy detected by magnetic resonance angiography (MRA), c) are receiving blood transfusions for ≥1 year, and d) express a desire to discontinue blood transfusion therapy. Regular blood transfusions are suggested to be continued indefinitely for children who have evidence of silent cerebral infarcts or vasculopathy based on MRI and MRA findings. In low-middle-income areas where regular blood transfusions are inaccessible or financially burdensome, the guideline suggested the use of hydroxyurea at a fixed-dose of at least 20 mg/kg daily or the maximum tolerated dose for children with abnormal TCD results. For secondary stroke prevention, regular blood transfusions are recommended for children with SCD genotypes HbSS or HbSβ^0-thalssemia who have previously experienced an ischemic stroke. In cases where children are unable to undergo or decline blood transfusions for secondary stroke prevention, the ASH acknowledged that hydroxyurea is an inferior substitute compared to regular blood transfusions, but it is superior to no treatment.[51] The ASH guideline does not go so far as to make a recommendation regarding hydroxyurea as an alternative option for secondary stroke prevention.

Generally, patients with SCD should be initiated and optimized on the standard of care “(eg, HU [hydroxyurea], L-glutamine, crizanlizumab, and chronic transfusion therapy)” before proceeding to hematopoietic stem cell transplantation (HSCT); the exception may be for patients who have a history of overt stroke or abnormal TCD results.[45] Patients who have a suboptimal or lack of response to the

standard of care, or those who persistently experience recurrent ACS despite receiving optimized standard treatments may be evaluated for the possibility of matched-related allogeneic transplantation.[45]

Table 4 provides an overview of the guideline recommendations for disease-targeted pharmacotherapies, primarily hydroxyurea, as guidelines seldom mention newer agents.

Table 4. Guideline Recommendations for Disease-targeted Pharmacotherapies for the Treatment of Sickle Cell Disease

Professional organization and guideline (published year)	**Guideline recommendations for disease-targeted agents** *(Recommendation strength; evidence quality)*[a]

National Heart, Lung, and Blood Institute (**NHLBI**)[b]
 	
Evidence-based management of sickle cell disease: expert panel report (2014)[35]
	Hydroxyurea
	
	<u>General Recommendations:</u>
	• All patients diagnosed with SCA and their family members should be counseled on the therapeutic use of hydroxyurea *(consensus-panel expertise)*
	• To ensure optimal utilization of hydroxyurea and to maximize its therapeutic benefits and safety, it is recommended to adhere to a well-established monitoring and prescribing protocol *(strong; high)*
	• Hydroxyurea should be discontinued in pregnant or breastfeeding women *(moderate; very low)*
	• Patients with genotypes HbSC or HbSβ$^+$-thalassemia whose daily activities or quality of life are impacted by recurrent sickle cell-related pain should consult a specialist in SCD for consideration of hydroxyurea *(moderate; low)*
	• Patients who fail to achieve a clinical response with hydroxyurea after receiving the appropriate dose and duration should seek consultation with a SCD specialist *(moderate; very low)*
	<u>Recommendations for Adults and Children:</u>
	• To improve signs and/or symptoms of anemia, hydroxyurea can be added to erythropoietin in adults and children with SCD and comorbid CKD *(weak; low)*
	<u>Recommendations for Adults Only:</u>
	• Hydroxyurea is recommended for adults with SCA, and at least 1 of the following criteria:
	  ○ who experience ≥3 moderate to severe sickle cell pain crises within a one-year period *(strong; high)*
	  ○ whose daily activities and/or quality of life are impacted by sickle cell-associated pain *(strong; moderate)* or who have severe symptomatic chronic anemia *(strong; moderate)*
	  ○ who have a history of recurrent and/or severe acute chest syndrome *(strong; moderate)*
	<u>Recommendations for Infants, Children, and Adolescents Only:</u>
	• Irrespective of clinical severity, hydroxyurea should be offered to infants aged ≥9 months, children, and adolescents with SCA to decrease complications of SCD (*strong; high*: ages 9 to 42 months; *moderate; moderate*: ages >42 months)

[a] *See **Appendix C** for details about the recommendation strength and quality of evidence*

[b] *Guideline experts define sickle cell anemia (SCA) as having genotypes HbSS or HbSβ^0-thalassemia[34]*

Abbreviations: ACS, acute chest syndrome; ASH, American Society of Hematology; ATS, American Thoracic Society; CKD, chronic kidney disease; Hb, hemoglobin; HbF, fetal hemoglobin; HLA, human leukocyte antigens; HSCT, hematopoietic stem cell transplantation; MRA, magnetic resonance angiography; NHLBI, National Heart, Lung, and Blood Institute; PAH, pulmonary arterial hypertension; SCA, sickle cell anemia; SCD, sickle cell disease; TCD, transcranial Doppler ultrasound; VOCs, vaso-occlusive crises

Table 4. Guideline Recommendations for Disease-targeted Pharmacotherapies for the Treatment of Sickle Cell Disease

Professional organization and guideline (published year)	**Guideline recommendations for disease-targeted agents** *(Recommendation strength; evidence quality)*[a]
American Thoracic Society (**ATS**) Diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease (2014)[49]	**Hydroxyurea** • Hydroxyurea is recommended in children and adults with SCD and an increased mortality risk (defined as those with confirmed pulmonary hypertension by right heart catheterization, a tricuspid regurgitant jet velocity of ≥2.5 m/s, or an N-terminal pro-brain natriuretic peptide of ≥160 pg/mL) (*strong; moderate*) o If the patient is not a candidate for, or fails to respond to hydroxyurea, chronic transfusions are suggested as an alternative option (*weak; low*)
American Society of Hematology (**ASH**) Guidelines for sickle cell disease: cardiopulmonary and kidney disease (2019)[52]	**Hydroxyurea** • Combination treatment with erythropoiesis-stimulating agents and hydroxyurea is suggested to be used in adults and children with SCD and worsening CKD-related anemia (*conditional; very low*) o Enhancing compliance to hydroxyurea for patients already taking erythropoiesis-stimulating agents can potentially maximize HbF responses in patients undergoing combination treatment o In patients taking erythropoiesis-stimulating agents, it is advised to not exceed a Hb threshold of 10 g/dL (30% hematocrit) to mitigate the potential risks of vaso-occlusion-related complications • Initiating or optimizing disease-modifying therapies (eg, hydroxyurea, chronic transfusions) should be considered for patients diagnosed with SCD and PAH (*ungraded statement*)
American Society of Hematology (**ASH**) Guidelines for sickle cell disease: management of acute and chronic pain (2020)[50]	**Hydroxyurea/ "Other disease-modifying therapies"** • In specific clinical scenarios where conventional interventions "(eg, hydroxyurea, other disease-modifying therapies)" have demonstrated limited effectiveness in managing recurring pain episodes, a trial of monthly blood transfusions may be considered provided comprehensive shared decision-making can be effectively implemented (*ungraded statement*)

[a] *See **Appendix C** for details about the recommendation strength and quality of evidence*

[b] *Guideline experts define sickle cell anemia (SCA) as having genotypes HbSS or HbSβ⁰-thalassemia*[34]

Abbreviations: ACS, acute chest syndrome; ASH, American Society of Hematology; ATS, American Thoracic Society; CKD, chronic kidney disease; Hb, hemoglobin; HbF, fetal hemoglobin; HLA, human leukocyte antigens; HSCT, hematopoietic stem cell transplantation; MRA, magnetic resonance angiography; NHLBI, National Heart, Lung, and Blood Institute; PAH, pulmonary arterial hypertension; SCA, sickle cell anemia; SCD, sickle cell disease; TCD, transcranial Doppler ultrasound; VOCs, vaso-occlusive crises

Table 4. Guideline Recommendations for Disease-targeted Pharmacotherapies for the Treatment of Sickle Cell Disease

Professional organization and guideline (published year)	**Guideline recommendations for disease-targeted agents** *(Recommendation strength; evidence quality)*[a]
American Society of Hematology (**ASH**) Guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults (2020)[51]	**Hydroxyurea** <u>Primary stroke prevention in children (aged 2 to 16 years) with SCD, including HbSS and HbSβ⁰-thalassemia genotypes:</u> • Hydroxyurea, at the highest tolerated dosage, is suggested to be considered as a substitute for regular blood transfusions in children with abnormal TCD results, who have been receiving transfusions for ≥1 years, no MRA-defined vasculopathy or silent cerebral infarcts, and express a desire to discontinue blood transfusion therapy (*conditional; low*) • Hydroxyurea, at a fixed-dose of at least 20 mg/kg daily or the maximum tolerated dose, is suggested to be used in those who have abnormal TCD results and are residing in low-middle-income areas where chelation treatment or regular blood transfusion therapy are either inaccessible or financially burdensome (*conditional; low*) <u>Secondary stroke prevention in children with SCD (genotypes HbSS or HbSβ⁰-thalassemia only):</u> • For children with SCD and genotypes HbSS or HbSβ⁰-thalassemia who are unable to undergo or decline transfusions for secondary stroke prevention, hydroxyurea is an inferior substitute to regular blood transfusions, but is superior to no treatment (*ungraded statement*)
American Society of Hematology (**ASH**) Guidelines for sickle cell disease: stem cell transplantation (2021)[45]	**Standard of care (eg, hydroxyurea, L-glutamine, and crizanlizumab)** • Patients with SCD and a history of overt stroke or have abnormal TCD results are suggested to be treated with HLA-matched-related HSCT instead of standard of care (hydroxyurea or blood transfusions) (*conditional; very low*) • Matched-related allogeneic transplantation may be considered for patients who have a suboptimal, or lack of response to the standard of care (eg, "hydroxyurea, new targeted therapies or chronic transfusion therapies" [page 3676]) (*ungraded statement*) • Patients who persistently experience recurrent ACS despite receiving optimized standard treatments "(eg, HU [hydroxyurea], L-glutamine, crizanlizumab, and chronic transfusion therapy)" (page 3670) may be evaluated for the possibility of matched-related allogeneic transplantation (*ungraded statement*)

[a] *See **Appendix C** for details about the recommendation strength and quality of evidence*

[b] *Guideline experts define sickle cell anemia (SCA) as having genotypes HbSS or HbSβ⁰-thalassemia[34]*

Abbreviations: ACS, acute chest syndrome; ASH, American Society of Hematology; ATS, American Thoracic Society; CKD, chronic kidney disease; Hb, hemoglobin; HbF, fetal hemoglobin; HLA, human leukocyte antigens; HSCT, hematopoietic stem cell transplantation; MRA, magnetic resonance angiography; NHLBI, National Heart, Lung, and Blood Institute; PAH, pulmonary arterial hypertension; SCA, sickle cell anemia; SCD, sickle cell disease; TCD, transcranial Doppler ultrasound; VOCs, vaso-occlusive crises

7.0 SUMMARY OF L-GLUTAMINE, VOXELOTOR, AND CRIZANLIZUMAB PIVOTAL CLINICAL TRIALS

We identified one pivotal randomized controlled trial (RCT) each for L-glutamine and crizanlizumab (SUSTAIN),[53,54] and two trials for voxelotor (HOPE and HOPE-KIDS 1).[7,55] Out of the 4 identified RCTs, 2 trials were phase 3 (L-glutamine and HOPE),[7,54] and 2 trials were phase 2 (SUSTAIN and HOPE-KIDS 1).[53,55] Except for HOPE-KIDS 1, all of these trials were placebo-controlled.[7,53-55] Although HOPE-KIDS 1 is an ongoing, phase 2a dose-finding pharmacokinetic study, details on the interim results are provided because voxelotor was granted accelerated approval by the FDA based on these findings in children 4 to <12 years of age.[55] **Table 5** highlights key study characteristics of each trial (refer to the study-specific sections of this report and/or **Table 7** for additional details). Although the efficacy and safety of the lower dosages of crizanlizumab and voxelotor are summarized below, only the higher dosages (ie, voxelotor 1500 mg, crizanlizumab 5 mg/kg) are FDA approved for the treatment of SCD.

Table 5. Study Design and Medication Dosing Characteristics of the Pivotal Clinical Trials for Newer Sickle Cell Disease-targeting Agents

Study agent	RCT name	Study phase (treatment duration)	Study groups (sample size)	Primary outcome
L-glutamine	L-Glutamine in Sickle Cell Disease[54]	Phase 3 (48 weeks)	L-glutamine (PO BID): 0.3 g/kg/dose (n=152) Placebo (PO BID): n=78	Number of pain crises
Voxelotor	HOPE[7]	Phase 3 (up to 72 weeks)	Voxelotor (PO once daily): • 900 mg (n=92) • 1500 mg (n=90) Placebo (PO once daily): n=92	Proportion of participants who had a Hb response[a]
	HOPE-KIDS 1[55]	Phase 2a (48 weeks)	Voxelotor (PO once daily): weight-based dosing consistent with product labeling (n=45)	
Crizanlizumab	SUSTAIN[53]	Phase 2 (52 weeks)	Crizanlizumab (IV q4w): • 2.5 mg/kg (low dose; n=66) • 5 mg/kg (high dose; n=67) Placebo (IV q4w): n=65	Yearly rate of sickle cell pain crises

[a] *Hemoglobin (Hb) response was defined as >1 g/dL increase in baseline Hb to week 24.[7,55] The primary outcome of the HOPE-KIDS 1 trial was not explicitly stated in the publication, but this appears to be a main outcome.*

Abbreviations: BID, twice daily; Hb, hemoglobin; IV, intravenously; PO, orally; q, every; RCT, randomized controlled trial; w, week

7.1 Study population among the pivotal clinical trials

All participants were diagnosed with SCD, but the genotype of SCD varied across trials: participants with HbSS or HbSβ^0-thalassemia were enrolled in the HOPE-KIDS 1 and L-glutamine RCT,[54,55] whereas those with any SCD genotype were allowed to participate in the SUSTAIN and HOPE trials.[7,53] The laboratory test for Hb variant analysis also varied across trials: the L-glutamine RCT used Hb electrophoresis,[54]

HOPE used HPLC or thin layer isoelectric focusing with confirmatory DNA testing if required,[56] and SUSTAIN used HPLC[57]; information about Hb variant detection was not reported for the HOPE-KIDS 1 trial.[55]

In all studies, concomitant hydroxyurea use was permitted, but enrolled participants must have been on a stable dose for ≥3 months.[7,53-55] In most of the trials, around 66% of enrolled participants were taking hydroxyurea as background treatment.[7,53,54] Notably, in the HOPE-KIDS 1 trial, a higher proportion of participants (84%) were concomitantly using hydroxyurea, but that may have been influenced by the smaller sample size (n=45).[55] No trial addressed concomitant use with another SCD disease-modifying agent other than hydroxyurea. Except for HOPE-KIDS 1, all of the RCTs required participants to have experienced ≥1 (HOPE) or ≥2 (SUSTAIN and L-glutamine RCT) sickle cell pain crises, also referred to as VOCs, within the previous 12 months.[7,53-55] SUSTAIN and HOPE had an upper threshold of 10 VOCs in the previous year permitted,[7,53] whereas the L-glutamine RCT had no upper limit.[54] HOPE-KIDS did not have specific inclusion criteria regarding previous VOCs, but approximately 53% of enrolled participants experienced ≥1 VOC in the prior 12 months.[55]

Table 6 provides an overview of the key inclusion criteria for patients enrolled in the pivotal clinical trials. See **Appendix D** for additional inclusion criteria, and exclusion criteria.

Table 6. Overview of the Patient Population in the Pivotal Clinical Trials for L-glutamine, Voxelotor, and Crizanlizumab

RCT	Select inclusion criteria		
	Age	***SCD genotype(s)***	***Number of VOCs[a] within the previous 12 months***
L-glutamine in Sickle Cell Disease[54]	≥5 years	HbSS or HbSβ^0-thalassemia	≥2
Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease (SUSTAIN)[53]	16 to 65 years	Any SCD genotypes including HbSS, HbSC, HbSβ^0-thalassemia, HbSβ$^+$-thalassemia	2 to 10
A Phase 3 Randomized Trial of **Voxelotor** in Sickle Cell Disease (HOPE)[7]	12 to 65 years	Any SCD genotypes including HbSS, HbSC, HbSβ^0-thalassemia, HbSβ$^+$-thalassemia	1 to 10
Safety and Efficacy of **Voxelotor** in Pediatric Patients with Sickle Cell Disease Aged 4 to 11 Years (HOPE-KIDS 1)[55]	4 to 11 years	HbSS or HbSβ^0-thalassemia	--

[a] *For some of the studies, this was referred to as sickle cell pain crises. The definition of the event varied slightly from each trial, but generally referred to an acute pain episode requiring the administration of analgesics in a health care setting.*[7,53,54,58]

Abbreviations: approx., approximately; Hb, hemoglobin; RCT, randomized controlled trial; SCA, sickle cell anemia; SCD, sickle cell disease; VOCs, vaso-occlusive crises

7.2 Pivotal clinical trial for L-glutamine

Niihara et al (2018) conducted a 53-week, multicenter, randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of L-glutamine among patients ≥5 years of age with SCD, specifically genotypes HbSS or HbSβ^0-thalassemia confirmed by Hb electrophoresis, who experienced at least 2 sickle cell pain crises within the previous 12 months.[54] Patients on stable doses of hydroxyurea (for ≥3 months before enrollment) were allowed to enter the study and continue hydroxyurea as background therapy.[54]

Participants were randomized in a 2:1 ratio to receive twice daily oral doses of L-glutamine (n=152; 0.3 g/kg/dose, up to 30 g daily) or placebo (n=78) over 48 weeks, followed by a 3-week tapering phase.[54] Across both study groups, approximately 66% of participants were concomitantly taking hydroxyurea. The median age for participants treated with L-glutamine was 19 years (range 5 to 57 years) and around half (51%) were over 18 years of age. Most participants were Black (95%), had genotype HbSS (90%), and experienced 2 to 5 sickle cell pain crises in the previous 12 months (84%). In the L-glutamine and placebo arms, baseline Hb levels were 8.8 g/dL and 8.7 g/dL, respectively. The primary endpoint was the mean number of pain crises from the time of starting study treatment through 48 weeks.[54]

L-glutamine significantly reduced the occurrence of sickle cell pain crises (see note[†]) compared to placebo (median number of crises events over 48 weeks of treatment: 3 vs. 4, respectively), resulting in a 25% reduction.[54] Furthermore, L-glutamine-treated participants experienced significantly fewer hospitalizations for sickle cell-related pain relative to placebo-treated participants at week 48 (median of 2.3 vs. 3.0, respectively). Additionally, the median time to the first and second pain crisis were significantly longer for those receiving L-glutamine compared to placebo. Based on a subgroup analysis, hydroxyurea had no effect on the observed clinical benefit shown with L-glutamine.[54]

The FDA noted that the results observed for in this study may have been biased due to the imputation methods that were used to address the high and differential attrition rate in the study[26,59]; the discontinuation rate was 36.2% in the L-glutamine arm and 24.4% in the placebo arm,[60] with reasons for early withdrawal similar among treatment groups and generally unrelated to the intervention.[54] The FDA performed multiple sensitivity analyses and concluded that L-glutamine is likely to offer a benefit, but the magnitude tends to be modest,[59] and is sensitive to the analytic methods used.[26]

Overall, numerically more adverse events (AEs) were reported in the placebo group compared to L-glutamine, including serious adverse events (SAEs).[54] The most frequently reported AEs among the L-glutamine arm with a ≥5% difference compared to placebo were nausea, back pain, and extremity (leg or arm) pain. Within the study period, two participants with a history of chronic organ failure, randomized to the L-glutamine arm, experienced sudden cardiac death. Authors concluded that the cause of death was unlikely to be related to L-glutamine.[54]

[†] Sickle cell pain crises was defined as pain that resulted in parenterally-administered ketorolac or narcotics within a health care facility (ie, hospital, clinic, emergency department).[54]

7.3 Pivotal clinical trial for crizanlizumab (SUSTAIN)

SUSTAIN was a 52-week, multicenter, randomized, double-blind, placebo-controlled, phase 2 trial assessing the efficacy and safety of two different dosages of crizanlizumab (low- and high-dose) among patients (aged 16 to 65 years) with any genotype of SCD (eg, HbSS, HbSC, Hbβ^0-thalassemia), detected by HPLC.[53,57] Concomitant hydroxyurea was permitted for those with ≥6 months of use and on a stable dose for ≥3 months before enrollment; dosage adjustments during the 52-week trial period were not allowed except for safety concerns.[53] Participants were not allowed to start hydroxyurea during the study, and were required to demonstrate between 2 to 10 sickle cell pain crises within the previous 12 months to be eligible for the study.[53]

Participants were randomized in a 1:1:1 ratio to receive crizanlizumab 5 mg/kg (high-dose; n=67), crizanlizumab 2.5 mg/kg (low-dose; n=66), or placebo (n=65).[53] A total of 14 doses were administered intravenously over a 30-minute infusion during the 52-week treatment period: 2 loading doses were administered two weeks apart, followed by the maintenance dose every 4 weeks thereafter. The median age for participants treated with crizanlizumab (both high- and low-dose) was 29 years. Most participants were Black (92%), had genotype HbSS (71%), and experienced 2 to 4 sickle cell pain crises within the previous 12 months (63%). Across all treatment groups, about 62% of participants were taking hydroxyurea concomitantly with the study drug.[53]

Compared to placebo, high-dose crizanlizumab (5 mg/kg) significantly decreased the median annual rate of sickle cell pain crises (see note[‡]) at the end of the 52-week treatment period, representing a 45% reduction among the intention-to-treat (ITT) population.[53] Although a reduction in the median annual crises rate was observed with low-dose crizanlizumab (2.5 mg/kg), it did not reach statistical significance compared to placebo. Results of the primary endpoint for the high-dose group were further supported by sensitivity analysis in the per-protocol population. Subgroup analyses showed that hydroxyurea modified results: the annual pain crises rate for high-dose crizanlizumab was 32.1% lower than placebo among participants concomitantly taking hydroxyurea, and 50.0% lower than placebo among participants who were not taking hydroxyurea. Based on the number of pain crises in the previous year, high-dose crizanlizumab reduced the median rate of crises per year compared to placebo in participants who experienced 2 to 4 crises (1.14 vs. 2.0, respectively) or 5 to 10 crises (1.97 vs. 5.32, respectively). Additionally, compared to placebo, the rate of annual crises was reduced by 34.6% among high-dose crizanlizumab-treated participants with HbSS genotype, and 50.5% lower among those with a non-HbSS genotype (eg, HbSβ^0-thalassemia, HbSC).[53]

High-dose crizanlizumab, versus placebo, significantly increased the median time to a first (4.07 vs. 1.38 months, respectively) and second (10.32 vs. 5.09 months, respectively) pain crisis, and significantly reduced the rate of yearly uncomplicated crises (1.08 vs. 2.91).[53] It is unclear whether concomitant hydroxyurea use impacted the results of these secondary endpoints.

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‡ The yearly rate of sickle cell pain crises was the primary endpoint of SUSTAIN. Sickle cell pain crises was defined as acute pain episodes due to vaso-occlusion that necessitates the utilization of oral or parenteral narcotics, or parenteral nonsteroidal anti-inflammatory drugs (NSAIDs) within a medical facility. Crises events also extended to incidences of ACS, splenic or hepatic sequestration, and priapism.[53]

Overall, the number of participants who reported at least one SAE were comparable across treatment groups.[53] AEs reported more frequently (≥5% difference from placebo in either active-treatment arm) among crizanlizumab-treated participants were nausea, arthralgia, and diarrhea. Pyrexia (3%) and influenza (5%) occurred at numerically higher rates in the active-treatment groups compared to placebo. During the study, 3 participant deaths occurred,[53] but study investigators considered the causes to be unrelated to the study treatment.[26] Detectable antibodies to crizanlizumab did not develop in any of the participants during the trial.[53]

A post hoc assessment showed that numerically higher proportions of participants treated with crizanlizumab 5 mg/kg were VOC event-free compared to placebo (35.8% vs. 16.9%) during the experimental period.[61] This trend was consistent in subgroup assessments based on baseline VOC category and SCD genotypes. Additionally, compared to placebo, crizanlizumab demonstrated an increased median time to first VOC across all subgroups, with the most substantial increase shown in those with HbSS (1.12 months vs. 4.07 months, respectively) and those who were not using hydroxyurea concurrently (2.86 months vs. 5.68 months, respectively).[61]

7.4 Pivotal clinical trials for voxelotor (HOPE and HOPE-KIDS 1)

7.4.1 HOPE trial

HOPE was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of two dosages of voxelotor (900 mg and 1500 mg) compared to placebo, over a treatment period of up to 72 weeks.[7] Eligible participants (aged 12 to 65 years) had any genotype of SCD (eg, HbSS, HbSC, Hbβ^0-thalassemia) detected by HPLC or thin layer isoelectric focusing with confirmatory genetic testing if required,[56] a history of 1 to 10 VOCs within the previous 12 months, and a baseline Hb level of 5.5−10.5 g/dL. Participants who were already taking hydroxyurea were allowed to continue the agent during the trial as long as they were on a stable dose for ≥3 months.[7]

Participants were randomized in a 1:1:1 ratio to oral voxelotor (1500 mg [n=90] or 900 mg [n=92]), or placebo (n=92), taken once daily.[7] The median age of participants who received voxelotor was 24 years (range 12 to 59 years), and 84% were 18 years of age or older. Most participants were Black (66%), followed by Middle Eastern or Arab (22%) descent. Additionally, most participants had SCD genotype HbSS, and about two-thirds were taking hydroxyurea at baseline. Although baseline characteristics were generally comparable across arms, a higher percentage of participants had HbSS (80%) in the placebo group than voxelotor groups: 1500 mg (68%) and 900 mg (77%).[7]

Among the ITT population, significantly more participants treated with high-dose voxelotor (1500 mg) achieved an Hb response (defined as >1 g/dL increase in baseline Hb) at week 24 compared to placebo (51% vs. 7%, respectively; primary endpoint); 38% of participants treated with voxelotor 900 mg achieved a Hb response at week 24.[7] Consistent results were observed in a sensitivity analysis among the per-protocol population, showing a higher proportion of participants achieving a Hb response with voxelotor 1500 mg compared to placebo, irrespective of baseline anemia severity and concomitant hydroxyurea use. The adjusted mean change in Hb from baseline to week 24 was 1.1 g/dL (P<0.001) in the voxelotor 1500 mg group and −0.1 g/dL in the placebo group. Additionally, high-dose voxelotor (1500 mg) significantly impacted select laboratory markers of hemolysis (ie, indirect bilirubin, change in the percentage of reticulocytes) compared to placebo from baseline to week 24. Interestingly, red blood

cell transfusions were administered numerically more frequently among participants treated with voxelotor (32%−33%) compared to placebo (25%), primarily due to acute VOC. The annualized adjusted VOC incidence rate was numerically lower in those who received voxelotor versus placebo, with a similar trend in the subgroup with a history of ≥2 crises in the past 12 months.[7]

Overall, the rates of AEs and SAEs were comparable across all study groups.[7,58] The most frequently reported AEs among voxelotor recipients, with a ≥5% difference from placebo, were diarrhea, nausea, and abdominal pain.[7] Few participants experienced serious, treatment-related TEAEs: 3% in both the voxelotor arms and 1% in the placebo arm.[7] Although the overall number of participants discontinuing treatment due to an AE was low across all groups, the incidence was numerically higher among those who received active-treatment than placebo.[58] During the trial, 4 participant deaths occurred: 1 in the 1500 mg voxelotor group, 1 in the 900 mg voxelotor group, and 2 in the placebo group; study investigators determined that the four deaths were unrelated to the study treatment.[7]

7.4.1.1 Long-term results from the HOPE trial

The pre-specified long-term efficacy outcomes of the HOPE trial were reported recently in a publication by Howard et al (2021).[62] Long-term efficacy outcomes included the change in Hb concentrations and hemolysis laboratory markers from baseline to week 72, annualized incidence of VOC, and patient disease status, measured by the provider-reported Clinical Global Impression of Change (CGI-C) scale. In addition, safety results were reported over the entire 72-week treatment period among the modified ITT population (received ≥1 treatment dose).[62]

Regarding the adjusted mean change in Hb level from baseline to week 72, voxelotor 1500 mg maintained a statistically significant difference from placebo (1 g/dL vs. 0 g/dL, respectively; p<0.0001); a significant difference was also observed with the 900 mg dose of voxelotor relative to placebo (p=0.014).[62] Voxelotor 1500 mg showed sustained significant improvements in certain hemolysis-related laboratory markers (ie, indirect bilirubin concentrations [−26.6%; 95% CI: −40.2 to −12.9] and change in the percentage of reticulocytes [−18.6%; 95% CI: −33.9 to −3.3]), as evaluated by the difference in the adjusted mean percentage change compared to placebo from baseline at week 72. Overall, 36% of participants received a red blood cell transfusion during the study in each of the treatment arms, including placebo. During the 72-week treatment period, the annualized incidence rate of VOC was 2.4 across both voxelotor arms and 2.8 in the placebo arm. The incidence of VOC was lowest among voxelotor-treated patients who had Hb concentrations ≥12 g/dL than those with lower Hb concentrations or who received placebo. As measured by the CGI-C scale, a significantly greater percentage of participants rated their disease status as “moderately improved” or “very much improved” with voxelotor 1500 mg (74%) versus placebo (47%).[62]

The incidence of any AEs was generally similar across study groups, but grade 1 and 2 events occurred more often in those who received 1500 mg or 900 mg of voxelotor compared to placebo (64% vs. 61% vs. 53%, respectively).[62] The most frequently reported AEs among voxelotor-treated participants (≥5% difference from placebo) were nausea and pyrexia. AEs that were grade 3 or 4 were rare (≤10% of participants), but overall anemia was the most frequent. The incidence of non-SCD-related SAEs were comparable among treatment groups and the rate of drug discontinuation due to an AE was low across all treatment groups. A total of 6 deaths, two participants in each group, occurred during the trial; study investigators deemed the deaths were unrelated to voxelotor or placebo.[62]

7.4.2 HOPE-KIDS 1 trial

HOPE-KIDS 1 is a phase 2a, multicenter, open-label, single-arm, four-part, single- and multiple-dose trial assessing the pharmacokinetics, efficacy, and safety of voxelotor for SCD in the pediatric population (aged 6 months to 17 years).[55] This trial is currently ongoing, with multiple phases (labeled A to D) that encompasses various age ranges and treatment regimens. Eligible participants for phase C of the trial were 4 to 11 years of age, had SCD genotype HbSS or HbSβ^0-thalassemia, and a baseline Hb ≤10.5 g/dL; notably, there was no inclusion criterion regarding the number of sickle cell pain crisis in the previous 12 months. Similar to the predecessor trial (HOPE), participants already taking hydroxyurea were allowed to continue it during the trial if they had been on a stable dose for ≥3 months, and did not anticipate having dosage changes during the trial period. Interim results from phase C were used to help establish the basis for the accelerated approval of voxelotor in children aged 4 to <12 years, and therefore are summarized below.[55]

Efficacy and safety results were evaluated in a cohort of 45 participants (as of September 30, 2020) who received ≥1 dose of once-daily oral voxelotor for a treatment duration of 48 weeks.[55] Voxelotor was administered as the dispersible tablets; dosing ranged from 600 mg to 1500 mg depending on weight and was consistent with product labeling.[15,55] The median age of participants at screening was 7 years (range 4 to 11 years).[55] The baseline mean Hb level was 8.6 g/dL, with a mean HbF percentage of 17.7%. Approximately 96% of participants had genotype HbSS, and approximately 84% were concomitantly taking hydroxyurea during the study. Almost half of participants had no history of VOCs in the prior 12 months.[55]

The treatment effect of voxelotor was noticeable as early as week 2, and was sustained to week 24.[55] Of the participants who had both baseline and week 24 Hb measurements (n=34), 47% achieved a Hb response (defined as >1 g/dL increase in baseline Hb) at week 24. Additionally, 35% and 21% achieved >1.5 g/dL and >2 g/dL increase in Hb level from baseline to week 24, respectively. Voxelotor also improved the mean percentage change from baseline at week 24 for hemolysis-associated laboratory markers, with the greatest effect on indirect bilirubin.[55]

Among the safety population (those who received ≥1 dose of voxelotor; n=45), 49% experienced any drug-related TEAE.[55] The most frequently reported drug-related TEAEs (≥5% of participants) included diarrhea (11%), rash (11%), vomiting (11%), abdominal pain (9%), and elevations in transaminases (9%); the majority of these AEs were classified as grade 1. Four participants temporarily reduced the dose of voxelotor due to drug-related TEAEs, with one participant ultimately discontinuing voxelotor due to allergic edema, sickle cell anemia with crisis, and pyrexia. A total of 10 participants discontinued the study early, with 3 participants discontinuing due to an AE. No deaths have occurred in the trial.[55]

Table 7 provides an overview of select efficacy results from the pivotal clinical trials for L-glutamine, crizanlizumab, and voxelotor. See **Appendix E** for additional study details including safety findings.

Table 7. Select Efficacy Outcomes of the L-glutamine, Crizanlizumab, and Voxelotor Pivotal Clinical Trials[a]

Trial name Study identification number, RCT design	**Intervention and comparator** number of participants (n)	**Select efficacy endpoint and study drug(s)**			
A Phase 3 Trial of L-Glutamine in Sickle Cell Disease (NCT01179217)[54] Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial	**Intervention:** • L-glutamine 0.3 g/kg PO twice daily (n=152) ○ Max dose: 30 g daily **Comparator:** • Placebo PO twice daily (n=78)	**Efficacy outcome:**	**L-glutamine**	**Placebo**	
		Number of pain crises over 48 weeks (median [range]) — *primary endpoint*: **Difference from placebo (p-value):**	**3** (0–15) 25% (p=0.005)	4 (0–15)	
		Number of sickle cell pain-related hospitalizations over 48 weeks (median [range]): **Difference from placebo (p-value):**	**2** (0–14) 33% (p=0.005)	3 (0–13)	
		Median time to the first pain crisis (95% CI):	84 days (62, 109)	54 days (31, 73)	
		Median time to the second pain crisis (95% CI):	212 days (153, 250)	133 days (115, 179)	
Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease (SUSTAIN; NCT01895361)[53] Phase 2, randomized, double-blind, placebo-controlled trial	**Intervention:** • Crizanlizumab 2.5 mg/kg IV for 14 doses (low-dose; n=66) • Crizanlizumab 5 mg/kg IV for 14 doses (high-dose; n=67) **Comparator:** • Placebo IV for 14 doses (n=65)	**Efficacy outcome:**	**High-dose crizanlizumab (5 mg/kg)**	**Low-dose crizanlizumab (2.5 mg/kg)**	**Placebo**
		Median annual rate of sickle cell pain crises over 52 weeks (ITT population[b]) — *primary endpoint:* **Difference from placebo (p-value):**	**1.63** −45.3 (p=0.01)	2.01 −32.6 (0.18)	2.98
		Annual rate of days hospitalized: **Difference from placebo (p-value):**	4.00 −41.8 (p=0.45)	6.87 0.0 (p=0.84)	6.87
		Median time to first pain crisis: Hazard ratio (95% CI, p-value):	**4.07** 0.50 (0.33, 0.74; p=0.001)	2.20 0.75 (0.52, 1.10; p=0.14)	1.38
		Median time to second pain crisis: Hazard ratio (95% CI, p-value):	**10.32** 0.53 (0.33, 0.87; p=0.02)	9.20 0.69 (0.44, 1.09; p=0.10)	5.09
A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease (HOPE; NCT03036813)[7,58] Phase 3, multicenter, international, randomized, double-blind, parallel-group, placebo-controlled trial	**Intervention:** • Voxelotor 1500 mg (n=90) PO once daily • Voxelotor 900 mg (n=92) PO once daily **Comparator:** • Placebo (n=92) PO once daily	**Efficacy outcome:**	**High-dose voxelotor (1,500 mg)**	**Low-dose voxelotor (900 mg)**	**Placebo**
		Percentage of participants who achieved a Hb response[c] at week 24 (ITT population[b]) — *primary endpoint* (95% CI):	**51% (41%, 61%)**	33% (23%, 42%)	7% (1%, 12%)
		Adjusted mean change in hemoglobin from baseline to week 24 (least-squares mean; 95% CI):	**1.1 g/dL (0.9, 1.4)**	0.6 g/dL (0.3, 0.8)	−0.1 g/dL (−0.3, 0.2)
		Annualized adjusted incidence rate of VOC (number of crises per person-year; 95% CI):	2.77 (2.15, 3.57)	2.76 (2.15, 3.53)	3.19 (2.50, 4.07)
		Percentage change in hemolysis-associated laboratory markers (95% CI):			
		Indirect bilirubin:	**−29.1 (−35.9, −22.2)**	−20.3 (−27.1, −13.6)	−3.2 (−1-.1, 3.8)
		Reticulocyte count:	**−19.9 (−29.0, −10.9)**	−1.3 (−.10.3, 7.7)	4.5 (−4.5, 13.6)
		Lactate dehydrogenase:	−4.5 (−11.9, 2.8)	1.4 (−5.9, 8.7)	3.4 (−4.0, 10.9)

[a] *See **Appendix E** for additional study findings*

[b] *The intention-to-treat (ITT) population included all participants who were randomized[7, 53]*

[c] *Defined as >1 g/dL increase in baseline Hb to week 24[7, 55]*

Bolded results are significantly different from placebo

Abbreviations: CI, confidence interval; dL, deciliter; g, grams; Hb, hemoglobin; ITT, intention-to-treat; IV, intravenously; kg, kilogram; mg, milligram; PO, orally; VOC, vaso-occlusive crises

Table 7. Select Efficacy Outcomes of the L-glutamine, Crizanlizumab, and Voxelotor Pivotal Clinical Trials[a]

Trial name Study identification number, RCT design	**Intervention and comparator** number of participants (n)	**Select efficacy endpoint and study drug(s)**	
Safety and Efficacy of Voxelotor in Pediatric Patients with Sickle Cell Disease Aged 4 to 11 Years (HOPE-KIDS 1; NCT02850406)[55] Phase 2a, ongoing, multicenter, open-label, single-arm, four-part, single- and multiple-dose study	**Intervention:** • Voxelotor weight-based dosing (n=45) ○ 10 to <20 kg: 600 mg once daily ○ 20 to <40 kg: 900 mg once daily ○ ≥40 kg: 1500 mg once daily **Comparator:** none	**Efficacy outcome (interim results for Phase C):**	**Voxelotor**
		Percentage of participants who achieved a Hb response[c] at week 24:	47%
		Change in Hb level from baseline to week 24:	1 g/dL
		Percentage change in hemolysis-associated laboratory markers (range):	
		Indirect bilirubin:	38.6% (−76.0% to 40.0%)
		Reticulocyte count:	−3.3% (−95.0% to 110.3%)
		Lactate dehydrogenase	2.6% (−36.6% to 44.2%)

[a] *See **Appendix E** for additional study findings*

[b] *The intention-to-treat (ITT) population included all participants who were randomized[7, 53]*

[c] *Defined as >1 g/dL increase in baseline Hb to week 24[7, 55]*

Bolded results are significantly different from placebo

Abbreviations: CI, confidence interval; dL, deciliter; g, grams; Hb, hemoglobin; ITT, intention-to-treat; IV, intravenously; kg, kilogram; mg, milligram; PO, orally; VOC, vaso-occlusive crises

8.0 SAFETY

Information in the following sections summarizes the commonly reported adverse events, contraindications for use, and warnings and precautions from the prescribing information for L-glutamine, voxelotor, and crizanlizumab.[14,15,17]

8.1 Common adverse events

According to product labeling, commonly reported adverse events (AEs) for L-glutamine, voxelotor, and crizanlizumab are as follows:

- L-glutamine (incidence ≥10% in clinical trials)[14]: constipation, headache, nausea, abdominal pain, extremity pain, cough, back pain, and chest pain
- Voxelotor[15]:
    - Adults and pediatric patients ≥12 years of age (incidence ≥10% with a >3% difference from placebo in the HOPE trial): diarrhea, headache, nausea, abdominal pain, rash, and pyrexia
    - Pediatric patients 4 to <12 years of age (incidence ≥10% in clinical trials): diarrhea, headache, abdominal pain, rash, pyrexia, and vomiting
- Crizanlizumab (incidence ≥10% in the SUSTAIN trial)[17]: nausea, abdominal pain, pyrexia, back pain, and arthralgia

8.2 Contraindications

Both L-glutamine and crizanlizumab have no contraindications for use.[14,17] Voxelotor is contraindicated in patients with a prior hypersensitivity reaction to the active ingredient or any excipients.[15]

8.3 Warnings and precautions

The following bullets briefly list warnings and precautions for the reviewed agents, with additional details provided below:

- L-glutamine: none
- Voxelotor: hypersensitivity, interference with HPLC
- Crizanlizumab: infusion-related reactions, automated platelet counts laboratory assessment

L-glutamine does not carry any warnings or precautions according to product labeling.[14]

Voxelotor carries a warning for hypersensitivity reactions, which may manifest as urticaria, facial swelling, eosinophilia, among other symptoms, and should be discontinued if a reaction occurs and not re-initiated.[15] Voxelotor may interfere with HPLC results when determining an Hb variant, so it should not be taken within 10 days immediately preceding the test.[15]

Crizanlizumab has a warning for the potential development of infusion-related reactions, often occurring during the first or second infusion, but can happen within 24 hours of administration.[17] For severe reactions, product labeling recommends stopping the infusion and considering discontinuing the agent permanently.[17] Severe reactions should be managed appropriately, but corticosteroids should be used

cautiously in patients with SCD except when clinically indicated (eg, anaphylaxis), presumably due to the potential risk of exacerbating vaso-occlusive episodes.[63] For mild-to-moderate infusion-related reactions, the infusion should be temporarily interrupted or infused at a slower rate, and symptomatic treatment should be started (eg, NSAIDs, antihistamines, opioids, acetaminophen, intravenous fluids, and/or oxygen). Pre-medicating and/or infusing crizanlizumab at a reduced rate should be considered for subsequent infusions. Patients should be monitored for and counseled on the signs and symptoms of infusion-related reactions (eg, pain at various locations, fever, chills, diarrhea, pruritus, sweating, dyspnea). Crizanlizumab also carries a warning for interfering with automated platelet counts (platelet clumping), specifically when blood samples are held in ethylenediaminetetraacetic acid (EDTA)-containing tubes, which may cause inaccurate results (eg, falsely reduced platelet counts). To mitigate this issue, blood samples should be processed within 4 hours of collection, or held in citrate-containing tubes. Peripheral blood smear analysis can be used to estimate the platelet count when necessary.[17] Although not listed as a labeled warning or precaution in the package insert, crizanlizumab has the potential to induce the development of autoantibodies against the drug.[17] The number of patients with SCD who have received crizanlizumab and have detectable antibodies against the agent has been low in clinical studies (0%−1.6%),[17] including in the pivotal SUSTAIN trial.[53]

9.0 PHARMACOKINETICS

The terminal half-life is about 1 hour for L-glutamine,[14] 38.7 hours for voxelotor,[15] and 11.2 days for crizanlizumab.[17] For L-glutamine, the mean peak concentration is 150 mcg/mL about 30 minutes after a single oral dose of 0.1 g/kg.[14] Following absorption into the plasma, voxelotor undergoes predominant distribution into red blood cells owing to its preferential binding affinity for Hb[15]; after oral administration of voxelotor, the median time to peak drug concentration (T_{max}) in plasma and whole blood was 2 hours, and the mean peak concentrations in red blood cells and whole blood occurred between 6 to 18 hours. Although the area under the curve (AUC) and C_{max} increased by 42% and 45%, respectively, in whole blood, and by 42% and 95%, respectively, in plasma, when voxelotor was taken with a high-fat, high-calorie meal compared to the fasted state, product labeling recommends it may be taken with or without food.[15] It is expected exogenous L-glutamine is metabolized similarly to endogenous L-glutamine by being used in the synthesis of essential biomolecules (eg, nucleotides, proteins) which is also the major route of elimination.[14] Voxelotor is extensively metabolized via oxidation and reduction, and glucuronidation, and predominately excreted in the feces (62.6% of the dose and metabolites).[15] Because crizanlizumab is a monoclonal antibody, and therefore a protein, it is anticipated to be metabolized via catabolic pathways into peptides.[17]

10.0 USE IN SPECIAL POPULATIONS

10.1 Pediatric patients

Of the newer disease-targeted agents that are reviewed in this report, voxelotor has been studied at the youngest pediatric age of 4 years old.[15] The remaining agents, L-glutamine and crizanlizumab have been studied in pediatric patients aged ≥5 years and ≥16 years, respectively.[14,17] The efficacy and safety of these agents in pediatric patients younger than the respective approved age for use has not been evaluated.[14,15,17]

10.2 Older adults

The clinical trials for L-glutamine, voxelotor, and crizanlizumab enrolled an insufficient number of older adults (those aged ≥65 years), therefore it is unclear whether the treatment response for older adults varies from younger patients.[14,15,17] However, specifically for L-glutamine, it is likely that older adults have a comparable response to younger patients, as suggested by clinical experience.[14] Generally, a more cautious approach should be used when selecting the initial dose in older adults, preferring to start at the lower end of the dosage range due to the higher prevalence of hepatic or renal dysfunction and comorbid diseases in this population.[14]

10.3 Pregnant patients

SCD can have negative impacts on pregnancy-related maternal and fetal outcomes.[15,17] For example, pregnant women with SCD have an increased risk for pre-eclampsia, eclampsia, VOC, and maternal mortality. There is also an increased fetal risk for low birth weight, preterm delivery, intrauterine growth restriction, and perinatal mortality.[15,17] These risks should be taken into consideration when deciding to continue or stop a medication during pregnancy. For L-glutamine, prescribing information does not comment on its use during pregnancy due to the lack of available human or animal data; notably, the phase 3 pivotal trial excluded pregnant women or those anticipating pregnancy.[14] Based on animal data, product labeling for voxelotor and crizanlizumab advise these agents to be taken during pregnancy only if the benefits outweigh the potential fetal and/or maternal risks.[15,17] Pregnant women taking crizanlizumab should be counseled on the potential for fetal harm[17]; stillbirths/abortions were increased in animal studies at doses approximately 2.8 times the maximum recommended human dose. Additionally, as a monoclonal antibody, it has the potential to be transferred through the placenta to the fetus.[17]

10.4 Breastfeeding patients

Due to the lack of human data about the transfer of L-glutamine and crizanlizumab into breast milk and the effects on milk production or the breastfed infant, product labeling advises weighing the advantages associated with breastfeeding against the mother's clinical requirement for the agent, as well as the potential negative effects on the breastfed infant.[14,17] Breastfeeding is advised against while taking voxelotor, and for at least 2 weeks following the last administration, due to the potential for the breastfed infant to experience serious adverse effects, including hematopoietic changes.[15]

10.5 Patients with renal or hepatic impairment

The product labeling for L-glutamine, voxelotor, and crizanlizumab does not recommend dosage adjustment for patients with renal impairment[14,15,17] but should be used cautiously. Additionally, no dosage adjustment is recommended for L-glutamine and crizanlizumab regarding patients with hepatic impairment.[14,17] Patients with severe hepatic impairment (Child Pugh C) taking voxelotor require a reduced dose (see **Table 3** for recommended dosing).[15]

Table 8 provides an overview of the drug information regarding the use of these agents in special populations.

Table 8. Use of L-glutamine, Voxelotor, and Crizanlizumab in Special Populations

	L-glutamine[14]	Voxelotor[15]	Crizanlizumab[17]

Pediatric patients	• Studied in pediatric patients 5 years of age and older with SCD
	  ○ Across 2 placebo controlled trials, 46 children aged 5 to <12 years old, and 64 adolescents aged 12 to <17 years old have been studied to establish the safety and effectiveness
	• Safety and effectiveness in children <5 years has not been studied
		• Studied in pediatric patients 4 years of age and older with SCD
		  ○ In the HOPE trial, 26 pediatric patients aged 12 to <17 years of age were enrolled
		  ○ In the phase 2 study, so far 45 pediatric patients 4 to <12 years of age were enrolled, along with 11 pediatric patients 12 to <17 years of age
		• Safety and efficacy profiles in children ages 4 years and older are considered comparable to adults and across pediatric age groups
			• Studied in pediatric patients 16 years of age and older with SCD
			  ○ In the SUSTAIN trial, 1 pediatric patient was enrolled who received crizanlizumab
			• Safety and effectiveness in children <16 years of age has not been studied

Older adults (≥65 years of age)	• An insufficient number of older adults were enrolled in the clinical trials • It seems that the response does not differ between older and younger individuals based on clinical experience	• An insufficient number of older adults were enrolled in the clinical trials	• An insufficient number of older adults were enrolled in the clinical trials
Pregnancy	• No available human or animal data	• Human data is lacking • No adverse developmental effects were observed in embryo-fetal animal studies with pregnant rats and rabbits exposed up to 2.8 times and 0.3 times the MRHD, respectively, during organogenesis • Pregnant rats exposed to 2.8 times the MRHD resulted in reduced maternal and offspring body weights, and decreased offspring survival throughout the lactation period in an animal pre- and postnatal developmental study • Product labeling advises to take during pregnancy only if the benefits outweigh potential risks	• There is insufficient human data • Animal studies suggest potential fetal harm (increased risk of stillbirths/abortions) at 2.8 times the MRHD • Able to be transferred through the placenta to the fetus (effect was observed in infant monkeys) • Product labeling advises to take during pregnancy only if the benefits outweigh potential risks

Abbreviations: ESRD, end stage renal disease; MRHD, maximum recommended human dose; PK, pharmacokinetics; SCD, sickle cell disease

Table 8. Use of L-glutamine, Voxelotor, and Crizanlizumab in Special Populations

	L-glutamine[14]	Voxelotor[15]	Crizanlizumab[17]
Breastfeeding	• There is a lack of human data about the transfer of L-glutamine into breast milk and the effects on milk production or on the breastfed infant • Product labeling advises considering the risks versus benefits	• Excreted in the breast milk of animals (rats), and is likely to be present in human breast milk • **The manufacturer advises against breastfeeding while taking voxelotor, and for at least 2 weeks following the last administration**	• There is a lack of human data about the transfer of crizanlizumab into breast milk and the effects on milk production or on the breastfed infant • Maternal IgG is excreted into breast milk, and crizanlizumab is a IgG_2 monoclonal antibody • Product labeling advises considering the risks versus benefits
Renal impairment	• No dosage adjustment information is provided • Safety has not been determined	• No dosage adjustment information is provided • No clinically significant difference in PK was observed based on degree of renal impairment • Not studied in patients with ESRD requiring dialysis	• No dosage adjustment information is provided • The effect of renal impairment on PK parameters is unknown
Hepatic impairment	• No dosage adjustment information is provided • Safety has not been determined	• Dose should be decreased in patients with severe hepatic impairment (Child Pugh C; see **Table 3** for recommended dosing) • No dosage adjustment is needed for mild or moderate hepatic impairment	• No dosage adjustment information is provided • The effect of hepatic impairment on PK parameters is unknown

Abbreviations: ESRD, end stage renal disease; MRHD, maximum recommended human dose; PK, pharmacokinetics; SCD, sickle cell disease

11.0 DRUG INTERACTIONS

Product labeling for voxelotor recommends not taking this agent with strong or moderate cytochrome (CYP) 3A4 inducers due to the potential for decreased efficacy.[15] If concomitant use of a strong or moderate CYP 3A4 inducer is necessary, the dosage of voxelotor should be increased. Voxelotor should also be avoided when taking narrow therapeutic index sensitive CYP 3A4 substrates. Consider reducing the dose of the sensitive CYP3A4 substrate when co-administration is necessary.[15] As previously mentioned in **Section 8.3** (*warnings and precautions*), voxelotor and crizanlizumab have the potential to interfere with laboratory tests.[15,17] Product labeling recommends not taking voxelotor within 10 days immediately preceding an HPLC test.[15] For patients taking crizanlizumab requiring an automated platelet count, blood samples should be processed within 4 hours of collection, or held in citrate-containing tubes instead of EDTA-containing tubes. When necessary, peripheral blood smear analysis can be used to estimate the platelet count.[17] Drug interactions for L-glutamine remain to be determined because no interaction studies have been performed.[14] **Table 9** provides an overview of the drug interactions for voxelotor and crizanlizumab according to product labeling.

Table 9. Drug Interactions for Voxelotor and Crizanlizumab[a]

Voxelotor[15]
• **Interferes with HPLC testing for Hb genotype**: Avoid taking voxelotor within 10 days immediately preceding the test
• **CYP 3A4 inducers**: Avoid taking voxelotor with *strong* or *moderate* CYP 3A4 inducers ○ Concomitant use is necessary: the dose of voxelotor should be increased when co-administered with a CYP 3A4 inducer, as indicated below:
▪ **Strong CYP 3A4 inducers:** • 4 to <12 years of age, based on body weight: [b] ▪ 10 kg to <20 kg: 900 mg ▪ 20 kg to <40 kg: 1,500 mg ▪ ≥40 kg: 2,400 mg or 2,500 mg • ≥12 years of age: [b] ▪ 2,500 mg
▪ **Moderate CYP 3A4 inducer:** • 4 to <12 years of age, based on body weight: [b] ▪ 10 kg to <20 kg: 900 mg ▪ 20 kg to <40 kg: 1,200 mg ▪ ≥40 kg: 2,000 mg or 2,100 mg • ≥12 years of age: [b] ▪ 2,000 mg
• **Narrow therapeutic index CYP 3A4 sensitive substrates**: Avoid taking voxelotor with narrow therapeutic index sensitive CYP 3A4 substrates ○ Concomitant use is necessary: the dose of the sensitive CYP 3A4 substrate should be decreased
Crizanlizumab[17]
• **Interferes with automated platelet counts**: blood samples should be processed within 4 hours of collection or held in citrate-containing tubes

[a] *L-glutamine is not included in the table because drug interaction studies with this agent are lacking.*[14]

[b] *By mouth once daily*

Abbreviations: CYP, cytochrome; Hb, hemoglobin; HPLC, high-performance liquid chromatography

12.0 EXPERT OPINION GUIDANCE ON THE PLACE IN THERAPY FOR L-GLUTAMINE, VOXELOTOR, AND CRIZANLIZUMAB

A shared decision-making approach between the provider and patient should be used to determine which disease-modifying therapies to use that best align with the patient's values, preferences, and goals.[64] Hydroxyurea is typically considered the standard of care for patients with sickle cell anemia (SCA), denoted by experts as genotypes HbSS or HbSβ^0-thalassemia.[11,47,65] Given that there is less evidence on the therapeutic utility of hydroxyurea in patients with other SCD genotypes (eg, HbSC), experts advise using it on a case-by-case basis, weighing the benefits and risks.[11,66] Experts typically recommend add-on therapy to hydroxyurea with a newer agent regardless of SCD genotype.[66] According to expert opinion, L-glutamine, voxelotor, or crizanlizumab may be added to hydroxyurea, or may be used as an alternative option if the patient is unresponsive or intolerant to hydroxyurea.[64,66] Among the pivotal clinical trials for the newer agents, patients were able to continue hydroxyurea if they had been on a stable dose for ≥3 months.[7,53-55] Add-on therapy to optimized hydroxyurea with L-glutamine or crizanlizumab can be considered for patients who continue to experience VOCs.[66] Furthermore, add-on therapy with voxelotor may be considered for patients with persistent anemia.[47,64]

Based on our supplemental searches from 2022 to June 2023 for combination treatment evidence, and a recently published systematic review,[25] no clinical trials have evaluated the efficacy and safety of combination therapy with the newer SCD modulating agents (ie, L-glutamine, voxelotor, and crizanlizumab). Theoretically, combination use of these newer agents has the potential to selectively address the intricate pathophysiological mechanisms of SCD through diverse pathways.[64] Given the paucity of clinical evidence, some experts propose additive therapy according to risk stratification for SCD complications in patients with SCA.[47] As of now, the only available validated predictor of a negative SCA outcome is abnormal TCD velocity results, which identifies pediatric patients at high-risk for stroke.[47] However, more research is required to define validated markers for severity risk to stratify patients into risk categories.[47]

13.0 POTENTIAL BARRIERS TO RECEIVING NEWER AGENTS FOR SCD

Patients who experience barriers to care are likely to have suboptimal treatment and negative outcomes.[67-69] These barriers to care may include cost, insurance coverage, negative provider or patient attitudes, social stigma, limited access to SCD treatments, and lack of provider expertise or knowledge in treating SCD.[68-71] This report focuses on aspects of care related to the reviewed pharmacologic treatments; a follow-up report will address other potential barriers in further detail.

Hydroxyurea appears to have a suboptimal reputation in clinical settings. Results from a US survey study evaluating the perspectives of patients and providers found that hydroxyurea is often under-utilized for the treatment of SCD in children and adults.[71] According to provider survey respondents, approximately 23% of patients who were offered hydroxyurea were uninterested in taking the agent.[71] In turn, patients placed the barrier at the discretion of the providers. Of the participants who reported *not* taking hydroxyurea, the most common barrier was that their physician did not recommend it. The most common reason providers gave for not prescribing hydroxyurea was that there was "no indication" for hydroxyurea; even though over half the patients of these providers had SCD genotypes HbSS or HbSβ^0-thalassemia. Additional reasons for not prescribing hydroxyurea were reported by 11% of providers:

concerns about prescribing the medication for an SCD genotype with less evidence for use (eg, HbSC) or clinical appropriateness (due to pregnancy, kidney or liver issues), among other reasons.[71]

Another survey study from 2021 showed that hematologists and providers specialized in SCD were more comfortable treating patients with hydroxyurea, accompanied by opioids for pain management, than providers in other practice settings (eg, internal medicine, family medicine).[72] Barriers providers considered "very important" or "important" to prescribing hydroxyurea included patient concerns of potential adverse effects (eg, carcinogenesis, infertility in male patients), adherence to the medication and laboratory monitoring, lack of formal pediatric guidelines, and anticipation of pregnancy or lack of contraception use. Lack of provider awareness of recommendations for hydroxyurea use is also a barrier to utilization; obliviousness to the 2014 NHLBI guidelines for the management of SCD was reported by approximately 33% of provider respondents.[72] Interestingly, another descriptive study found that providers who were aware of the NHLBI guideline recommendations, including for hydroxyurea counseling and TCD screenings, would often not follow them because of preconceived perceptions that the patient would not adhere to the recommendations; discussion as to why the providers doubted the patients' ability to adhere to recommendations was not mentioned.[69]

The barriers to using the newer agents mostly encompass cost, insurance coverage, and resource utilization. Based on a 2022 SR, the most common identified patient barriers to starting L-glutamine were prior authorization (PA) denial for insurance coverage and a high deductible, reported by 38% and 21% of patients with SCD, respectively.[4] Similar insurance-related barriers were reported by patients starting voxelotor, including PA requirement and high co-pay. Common barriers associated with the utilization of crizanlizumab included insurance denial and issues with transportation to a medical facility to receive the infusion.[4] The cost-related barriers can be partially attributed to the availability of these newer medications only as brand-name products, under marketing exclusivity.[73-75] Hydroxyurea, the long-time standard of care, is available as generic.[76]

13.1 Discussion about potential barriers to SCD medication utilization

To contribute to the charges of Utah House Bill 487, the Drug Utilization Review (DUR) Board has been tasked with identifying potential barriers to patients with SCD accessing recommended treatments. The DUR Board may consider discussing the following potential barriers to Utah patients with SCD (with or without Medicaid coverage) regarding accessibility to L-glutamine, voxelotor, or crizanlizumab which are expensive medications[4]:

- All three agents appear to encounter insurance challenges (eg, denial of PA, high copay or deductible, delays in approval)
- According to prescribing information, crizanlizumab should be prepared and administered by a healthcare provider in a health care setting,[17] and some patients may face transportation barriers.[68]
- If hydroxyurea is required to be used before L-glutamine, voxelotor, or crizanlizumab, patient or provider resistance to hydroxyurea may translate to delays in receiving one of the newer agents. For example, some patients may be more hesitant to adhere to hydroxyurea than the newer agents because of side effects they have heard of that are associated with chemotherapeutic doses (eg, teratogenicity, malignancy).[47] To mitigate concerns and to help encourage consistent adherence, patients should be counseled about the lower dosing of hydroxyurea for SCD relative to chemotherapy and differences in expected side effects.[47]

Other considerations:

- The ethnic and racial demographic of patients with SCD is predominately Hispanic or African American[4,16]; these tend to be socioeconomically disadvantaged patient populations.[72]
    - Preconceived provider perceptions about race, ethnicity, and socioeconomic status may cause patients with SCD to experience disparities in care.[69]
- Only a limited number of providers specialize in SCD, and the majority of providers lack expertise in managing SCD. Therefore, patients with SCD who seek care from family medicine or non-hematology specialty providers are likely to encounter the barrier of provider inexperience with SCD treatment guidelines or recommended medications.

14.0 PRIOR AUTHROIZATION CRITERIA CONSIDERATIONS

Utah Medicaid currently has non-drug specific prior authorization (PA) criteria in place for rare disease medications (see **Appendix F** for the *Rare Disease Medications* form, version September 2022). Refer to **Appendix G** for drug-specific PA criteria considerations for L-glutamine, voxelotor, and crizanlizumab.

15.0 SUMMARY

Sickle cell disease (SCD) is characterized by acute and chronic complications (see **Table 2**) that affect numerous organ systems,[1,2,6] and can potentially lead to multi-organ failure if left untreated.[28] SCD comprises of several genetic hemoglobinopathies that result from the inheritance of two abnormal beta (β)-globin alleles: either two copies of HbS (ie, mutated alleles of Hb) or one copy of HbS with another abnormal gene variant (eg, HbC).[1,9,27,34] In general, patients with sickle cell anemia (SCA; typically interpreted as genotypes HbSS or HbSβ^0-thalassemia)[16,35] tend to have greater disease severity than those with other SCD genotypes (eg, HbSβ^+, HbSC).[8,26,27,36]

Hydroxyurea has been used for decades in the treatment of SCD.[11,31,65] It is approved specifically for SCA, but the indicated genotypes are not fully clarified or specified in the product labeling.[10,11,13,35,47] The 3 newer disease-modifying agents are indicated for SCD without specification to a particular genotype.[14,15,17] Pivotal studies for voxelotor (HOPE) and crizanlizumab (SUSTAIN) included patients with any SCD genotype with a certain number of vaso-occlusive crises (VOCs; at least 1 or 2, respectively) in the year prior to enrollment.[7,53] HOPE also required participants to have a Hb level of ≥5.5 to ≤10.5 g/dL during screening.[7] The pivotal phase 3 randomized controlled trial (RCT) for L-glutamine included patients with HbSS or HbSβ^0-thalassemia and at least 2 VOCs in the prior year to enrollment.[54]

Of the approved agents for SCD, crizanlizumab has the narrowest approved age for use (patients 16 years or older) while others have broader pediatric age ranges for use: hydroxyurea (as Siklos) is approved for patients ≥2 years of age, voxelotor for patients ≥4 years of age, and L-glutamine for patients ≥5 years of age.[13-15,17] Although these agents are approved for the treatment of SCD, the labeled indication varies according to the clinical objective:

- L-glutamine: to reduce sickle cell-related acute complications[14]
- Crizanlizumab: to decrease the frequency of VOCs[17]
- Voxelotor: does not indicate a particular clinical objective beyond the treatment of SCD, but mechanistically works by inhibiting HbS polymerization.[7,15]

- Hydroxyurea (Droxia, Siklos): to decrease the frequency of painful crises and the requirement for blood transfusions in patients with recurrent moderate to severe painful crises[10,13]

Results of the pivotal clinical trials showed that L-glutamine and crizanlizumab (at a dose of 5 mg/kg) significantly reduced the number of sickle cell pain crises or VOCs compared to placebo, regardless of concomitant hydroxyurea use.[53,54] Voxelotor (at a dose of 1,500 mg once daily) significantly improved Hb levels from baseline to week 24, increased the number of responders (with response defined as >1 g/dL), and improved certain laboratory markers of hemolysis (ie, indirect bilirubin, change in the percentage of reticulocytes) compared to placebo in patients ≥12 years of age[7]; the mean change in Hb levels from baseline, as well as hemolysis-associated laboratory markers, were sustained to week 72 in a long-term follow-up assessment.[62] In a phase 2, single-arm trial, voxelotor showed favorable outcomes in children aged 4 to 11 years.[55] Overall, L-glutamine, crizanlizumab, and voxelotor were well-tolerated, with no significant adverse effects reported.[7,53-55] Concomitant use of hydroxyurea was permitted in all of these trials; the majority of participants across these trials were taking hydroxyurea as background treatment during the experimental phase.[7,53-55]

Guidelines by the National Heart, Lung, and Blood Institute (NHLBI; 2014),[35] American Thoracic Society (ATS; 2014),[49] and American Society of Hematology (ASH; 2019–2021)[45,50-52] primarily address the use of hydroxyurea and do not provide specific recommendations for the newer agents. The NHLBI and ATS guidelines predate FDA approval of L-glutamine, voxelotor, and crizanlizumab.[35,49] The newer SCD guidelines by the ASH do not provide specific recommendations regarding the use of L-glutamine, voxelotor, or crizanlizumab[45,50-52]; however, the most recent ASH guideline from 2021 on stem cell transplantation included L-glutamine and crizanlizumab as part of the standard treatment approach for patients with certain complications (ie, recurrent acute chest syndrome).[45] The only FDA-approved curative treatment for SCD is hematopoietic stem cell transplantation (HSCT),[27,34,45] a procedure that comes with serious risks.[1,16]

There are several potential barriers to patients accessing L-glutamine, voxelotor, or crizanlizumab. A primary barrier may be the market cost of these brand-name only products, which prompts payer mechanisms to ensure proper prescribing of such therapy (eg, prior authorization). Patients for whom these agents are indicated may nonetheless run into prior authorization issues and high cost-sharing copays (or may lack insurance altogether). Crizanlizumab is slightly less accessible than the oral agents because it must be administered intravenously at a medical facility.[4,17] The more widespread barriers include the limited number of specialized SCD clinics and hematologists, as well as a lingering reluctance by providers and patients alike to use hydroxyurea, the mainstay of treatment.[68-71]

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APPENDIX A: LITERATURE SEARCH STRATEGIES

The tables below show our literature search strategies for randomized controlled trials (RCTs), as well as our supplemental searches in Embase and Ovid Medline for L-glutamine (Endari), voxelotor (Oxbryta), and crizanlizumab (Adakveo).

Table A1. Embase Literature Search Strategies: Primary Search May 11, 2023, Supplemental Search June 8, 2023

#	Searches	Results
	Primary search	
1	**'conference abstract'**/it OR **'conference review'**/it	4,780,058
2	**'l-glutam*'**:ti,ab,kw OR **'endari'**:ti,ab,kw OR **'voxelotor'**:ti,ab,kw OR **'oxbryta'**:ti,ab,kw OR **'gbt440'**:ti,ab,kw OR **'gbt-440'**:ti,ab,kw OR **'crizanlizumab'**:ti,ab,kw OR **'adakveo'**:ti,ab,kw OR **'seg101'**:ti,ab,kw OR **'seg-101'**:ti,ab,kw OR **'selg1'**:ti,ab,kw	17,104
3	**'glutamine'**/de OR **'voxelotor'**/de OR **'crizanlizumab'**/de	51,635
4	**#2** OR **#3**	65,304
5	**'sickle cell anemia'**/exp	47,625
6	**'sickle-cell'**:ti,ab,kw OR **'SCD'**:ti,ab,kw OR **'SCA'**:ti,ab,kw OR **'drepanocyt*'**:ti,ab,kw	71,257
7	((**'hemoglobin'** OR **'haemoglobin'**) NEXT/2 (**'disease*'** OR **'dysfunc*'** OR **'disorder*'**)):ti,ab,kw	2,731
8	**#5** OR **#6** OR **#7**	82,168
9	(**'crossover procedure'**:de OR **'double-blind procedure'**:de OR **'randomized controlled trial'**:de OR **'single-blind procedure'**:de OR **random***:de,ab,ti OR **factorial***:de,ab,ti OR **crossover***:de,ab,ti OR ((**cross** NEXT/1 **over***):de,ab,ti) OR **placebo***:de,ab,ti OR ((**doubl*** NEAR/1 **blind***):de,ab,ti) OR ((**singl*** NEAR/1 **blind***):de,ab,ti) OR **assign***:de,ab,ti OR **allocat***:de,ab,ti OR **volunteer***:de,ab,ti) AND [english]/lim	2,935,936
10	**#4** AND **#8** AND **#9**	194
11	**#10** NOT **#1**	**84**
	Supplemental search	
12	**'l-glutamine'**:ti,ab OR **'endari'**:ti,ab OR **'voxelotor'**:ti,ab OR **'oxbryta'**:ti,ab OR **'crizanlizumab'**:ti,ab OR **'adakveo'**:ti,ab	4,382
13	**#12** AND (**2022**:py OR **2023**:py)	**356**

Table A2. Ovid MEDLINE Literature Search Strategies: Primary Search May 11, 2023, Supplemental Search June 8, 2023

#	Searches	Results
	Primary search *Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to May 10, 2023*	
1	(**l-glutam*** or **endari** or **voxelotor** or **oxbryta** or **GBT440** or **GBT-440** or **crizanlizumab** or **adakveo** or **SEG101** or **SEG-101** or **Selg1**).ti,ab,kw,kf.	14,505
2	**glutamine**/ or **voxelotor**/ or **crizanlizumab**/	19,007
3	**1** or **2**	31,938
4	(**sickle-cell** or **SCD** or **SCA** or **drepanocyt***).ti,ab,kw,kf.	45,427
5	((**hemoglobin** or **haemoglobin**) adj2 (**disease*** or **dysfunc*** or **disorder***)).ti,ab,kw,kf.	2,711
6	exp **Anemia, Sickle Cell**/ or exp **Hemoglobin, Sickle**/	26,752
7	**4** or **5** or **6**	51,994
8	((**randomized controlled trial** or **controlled clinical trial**).pt. or **randomi?ed**.ab. or **placebo**.ab. or **clinical trials** as topic.sh. or **randomly**.ab. or **trial**.ti.) not (exp **animals**/ not **humans**.sh.)	1,444,102
9	**3** and **7** and **8**	35
	Supplemental search	
10	(**l-glutamine** or **endari** or **voxelotor** or **oxbryta** or **crizanlizumab** or **adakveo**).ti,ab.	3,129
11	Limit **10 to yr="2022-Current"**	284

APPENDIX B: SELECT PREVENTATIVE MEASURES

Summarized below are select preventative measures for patients with SCD; these recommendations include, but are not limited to the following:

Infection: Ensuring patients with SCD receive routine immunizations (eg, influenza, pneumococcal) is a vital component of preventive care in managing SCD due to the increased susceptibility of patients to acquire severe infections.[1,16,35] Furthermore, the 2014 National Heart, Lung, and Blood Institute (NHLBI) guideline recommends penicillin prophylaxis in children diagnosed with HbSS until at least 5 years of age (*strong recommendation*),[35] regardless if they have received pneumococcal immunizations (ie, PCV13 or PPSV23).[16] Except in cases where patients with HbSS have undergone splenectomy or experienced invasive pneumococcal infection, penicillin prophylaxis should be discontinued at age 5.[35] Typically, antibiotic prophylaxis is not prescribed for other types of SCD,[1,16] unless they have undergone a splenectomy.[35]

Preventive screening:

- **Vision:** Starting at age 10, children with SCD should receive dilated eye examinations (*strong recommendation*), at 1 to 2 year intervals if the examination results are normal.[35] Those suspected of having retinopathy should be referred to a retina specialist.[35]
- **Kidney:** The 2014 NHLBI guideline recommends children should be screened for kidney disease by evaluating the presence of proteinuria starting at age 10.[35] In the event of a negative result, annual repeat screening should be conducted. However, if the result is positive, a first morning void urine albumin-creatinine ratio should be performed. If abnormalities are detected, a renal specialist should be consulted or referred (*consensus-panel expertise*).[35]
- **Heart:** In individuals with SCD, routine electrocardiogram screening is not recommended for both pediatric and adult populations.[35] However, it is recommended to screen and appropriately treat hypertension in these populations (*consensus-adapted*).[35]
- **Lungs:** A comprehensive evaluation of respiratory disorders, including asthma, chronic obstructive pulmonary disease, restrictive lung disease, and obstructive sleep apnea, should be conducted in children and adults with SCD by assessing the patient's medical history and performing a physical examination.[35] Additional testing (eg, pulmonary function tests) is recommended to be performed in patients who have symptoms or signs of respiratory complications (*consensus-panel expertise*).[35]
- **Stroke:** Starting at age 2, it is recommended to screen children with SCA (HbSS or HbSβ^0-thalassemia) yearly using a transcranial Doppler ultrasound (TCD), and continuing until the patient is at least 16 years of age (*strong recommendation*).[35] As stroke prevention, children with abnormal results should be referred to a specialist for chronic blood transfusions,[1,35] with careful monitoring to prevent iron overload and other potential complications (eg, alloimmunization, hemolysis).[1,16,55] It is not recommended to perform screening with TCD in children with other SCD types (*strong recommendation*).[35]

APPENDIX C: GUIDELINE DEFINITIONS

Table C1. Definitions of Guideline Level of Evidence and Recommendation Strength

NHLBI; 2014[35]	
When determining the recommendation strength, the expert panel used a modified GRADE approach by introducing a third category, named "moderate" to the traditional GRADE framework classification of "strong" or "weak".[35]	
Strong recommendation	• Demonstrates benefits clearly outweigh the risks, or vice versa
Moderate recommendation	• Patients would experience improved outcomes by adhering to a recommendation, even though there existed some degree of uncertainty regarding the extent of the intervention's benefits or the relative advantages of alternative approaches • Quality of supporting evidence is not defined
Weak recommendation	• Suggests a equipoise may or may not, or definitely exists between the benefits and risks • Uncertainty in the estimate may exist depending on the quality of supporting evidence
Consensus recommendations • *Consensus-Panel Expertise* • *Consensus-Adapted*	• Based on expert opinion
High quality evidence	• "Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies"[35 a] • The confidence in the estimated effect is highly unlikely to change with subsequent research.
Moderate quality evidence	• "Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies"[35 a] • The confidence in the estimated effect is likely to be influenced by subsequent research, and may potentially change the estimate
Low quality evidence	• "Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence"[35 a] • The confidence in the estimated effect is highly influenced by subsequent research, and will probably change the estimate
Very low quality evidence	• "Evidence for at least one of the critical outcomes from unsystematic clinical observations or very indirect evidence."[35 a] • For at least one critical outcome, any effect estimation is highly uncertain
ATS; 2014[49,77]	
Recommendations were based on a GRADE approach; recommendation strength was classified as either strong or weak based upon the assessment of the evidence quality, balance between benefits and harms, patient preferences and values, and resource utilization. The evidence quality categories ranged from high to very low, and signifies the confidence in the effect estimates.	

[a] *Located in Exhibit 4 on page 7 of the 2014 NHLBI guideline on sickle cell disease[34]*

Abbreviations: ASH, American Society of Hematology; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NHLBI, National Heart, Lung, and Blood Institute; RCTs, randomized controlled trials

Table C1. Definitions of Guideline Level of Evidence and Recommendation Strength

Strong recommendation	• Clearly the benefits outweigh the harms or vice versa
Weak recommendation	• A lower degree of certainty exists whether benefits outweigh the harms or vice versa, or an equipoise exists between the benefits and harms
High quality evidence	• Well-conducted RCTs
Moderate quality evidence	• RCTs with important limitations (eg, methodology flaws, inconsistent results, high reporting bias), or well-controlled, strong observational studies (eg, large magnitude of effect, presence of a dose-response gradient)
Low quality evidence	• Observational studies, or RCTs with very severe limitations
Very low quality evidence	• Other study types (eg, case series, case reports) or poorly controlled observational studies
ASH; 2019[52], 2020[50,51]; 2021[45]	
Recommendations were based on a GRADE approach; recommendation strength was classified as either strong or conditional. Quality of evidence (termed certainty in the evidence) was evaluated based on the domains of imprecision, risk of bias, inconsistency, presence of large effects, indirectness, confounding, and others. The quality of evidence was assigned into 4 categories, ranging from very low to high (represented by symbols).	
Strong recommendation	• Denoted by the wording "recommends". • Most patients express a desire for the recommended course of action, and most providers should follow the recommendation
Conditional recommendation	• Denoted by the wording "suggests" • Many patients may not want the suggested recommendation, even though majority of individuals would • Providers should take into consideration the patient's preferences and values to determine an individualized decision
High quality evidence ⊕⊕⊕⊕	• Regarding the effects, there is a high certainty in the evidence
Moderate quality evidence ⊕⊕⊕◯	• Regarding the effects, there is moderate certainty in the evidence
Low quality evidence ⊕⊕◯◯	• Regarding the effects, there is low certainty in the evidence
Very low quality evidence ⊕◯◯◯	• Regarding the effects, there is very low certainty in the evidence

[a] *Located in Exhibit 4 on page 7 of the 2014 NHLBI guideline on sickle cell disease[34]*

Abbreviations: ASH, American Society of Hematology; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NHLBI, National Heart, Lung, and Blood Institute; RCTs, randomized controlled trials

APPENDIX D: ELIGIBILITY CRITERIA IN PIVOTAL CLINCIAL TRIALS FOR NEWER SICKLE CELL DISEASE AGENTS

Table D1. Inclusion and Exclusion Criteria from Pivotal Clinical Trials for L-glutamine, Voxelotor, and Crizanlizumab

Trial name Study identification number, RCT design	**Inclusion criteria**	**Exclusion criteria**
A Phase 3 Trial of L-Glutamine in Sickle Cell Disease (NCT01179217)[54] Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial	• Males or females at least 5 years of age • Diagnosed with HbSS or HbSβ⁰-thalassemia confirmed by Hb electrophoresis • Experienced ≥2 painful crises[a] within the previous 12 months • Individuals taking hydroxyurea must be on a stable dose for ≥3 months prior to the screening visit, with continual use during the study • Women of childbearing potential agree to use appropriate contraceptive methods for the entirety of the study period	• Non-sickle cell related hospitalization within 2 months prior to the screening visit • Prothrombin time INR >2 • Serum albumin <3 g/dL • Any blood products received within 3 week prior to the screening visit • Clinically significant hepatic or renal disease,[54] including uncontrolled liver disease or renal insufficiency[14,59] • Previously received L-glutamine, including any form of glutamine supplementation within 30 days prior to the screening visit • Use of an experimental or investigational agent, including anti-sickling medications within 30 days prior to the screening visit (exception is the use of hydroxyurea in children and adolescents)[78] • Pregnant or lactating women, or women who wish to become pregnant[14,78] • Participated in an investigational device or drug trial within the previous 30 days of the screening visit, or is currently enrolled in such trial[59,78] • Based on the investigator's opinion, factors that may interfere with the participant's ability to comply with trial requirements[59,78]

Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease (SUSTAIN; NCT01895361)[53,79]
 	
Phase 2, randomized, double-blind, placebo-controlled trial
	• Males or females 16 to 65 years of age
	• Diagnosed with, or a confirmed medical history of HbSS, HbSC, HbSβ⁰-thalassemia, HbSβ⁺-thalassemia, or other SCD genotypes
	  ○ Hb variant was determined by HPLC[57]
	• Experienced 2 to 10 sickle-cell pain crises[b] within the previous 12 months
	• For individuals taking hydroxyurea or erythropoietin, they must be on a stable dose of either agent for ≥3 months immediately preceding the initial dosing on Day 1 (must have been prescribed for ≥6 months)
	• For females, a negative serum pregnancy test prior to the screening visit, as well as a negative urine pregnancy test before randomization and administration of the initial dose on Day 1
	• Women of childbearing potential agree to use appropriate contraceptive methods for the entirety of the study period and for ≥4 weeks following the end of the study
	• No acute pathologic processes present on admission chest X-ray, taken within 3 months before Day 1
	• Clinically appropriate medical (eg, vital signs) and physical examinations, including electrocardiogram and laboratory results
		• Individuals receiving chronic red blood cell transfusions (simple or exchange), including for prophylactic purposes, or Hb A >20% of total hemoglobin
		• Anticipate receiving an exchange transfusion during the study period
		• Hb <4 g/dL
		• Those planning to start, discontinue, or change dosing of hydroxyurea during the study period (except for safety concerns)
		• Those anticipating to have a major surgical procedure during the study period
		• Taking chronic anticoagulation medications (eg, heparin, warfarin), except aspirin
		• Non-sickle cell related, poorly controlled, neurologic, cardiovascular, hepatic, renal, or endocrine conditions, including the following abnormal laboratory thresholds:
		  ○ Creatinine ≥1.2 mg/dL
		  ○ Direct bilirubin ≥2 mg/dL
		  ○ ALT ≥3 times ULN
		• Received cancer diagnosis within the previous 5 years (except in situ cervical cancers and non-

[a] *The definition of a pain crises (similarly referred to as VOCs) varied slightly across applicable pivotal clinical trials:*

- *L-glutamine trial: Pain episode necessitating the utilization of parenterally administered narcotics or ketorolac within the confines of an emergency department, outpatient facility, or during inpatient hospitalization.[50]*
- *Crizanlizumab trial (SUSTAIN): Acute pain episodes due to vaso-occlusion that necessitates the utilization of oral or parenteral narcotics, or parenteral NSAIDs within a medical facility. Crises events also extended to incidences of ACS, splenic or hepatic sequestration, and priapism.[49]*
- *Voxelotor trial (HOPE): Acute pain episodes or ACS due to vaso-occlusion that necessitates the utilization of prescribed, or physician-directed use of oral or parental opioids, ketorolac, or other analgesics to alleviate moderate-to-severe pain within the confines of a health care setting (eg, emergency department, hospital, outpatient clinic).[7, 57]*

[b] *The HOPE-KIDS 1 trial is currently ongoing, with multiple phases (labeled A to D) that encompasses various age ranges and treatment regimens. Because interim results from phase C of the trial was used to help establish the basis for the accelerated approval of voxelotor in children aged 4 to 11 years, key eligibility criteria for part C of the trial are reported.[51]*

Abbreviations: ACS, acute chest syndrome; ALT, alanine aminotransferase; dL, deciliter; g, gram; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HIV, human immunodeficiency virus; INR, international normalized ratio; m, meter; min, minute; mg, milligram; SCD, sickle cell disease; ULN, upper limit of normal; VOCs, vaso-occlusive crises

Table D1. Inclusion and Exclusion Criteria from Pivotal Clinical Trials for L-glutamine, Voxelotor, and Crizanlizumab

Trial name Study identification number, RCT design	**Inclusion criteria**	**Exclusion criteria**
	• Participants gave informed consent (or parental permission, if applicable)	melanoma skin cancer) • Experienced a stroke within the previous 2 years • Individuals with HIV infection (indicated by prior presence of HIV antibodies) • Use of an investigational agent within 30 days before Day 1, or plans to participate in an investigational drug study during the trial period • Tested positive (via urine drug test) for phencyclidine, cocaine, or amphetamines at the screening visit • Based on the investigator's opinion, a mental or physical condition that may interfere with the study, or any condition that may interfere with the participant's safety
A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease (HOPE; NCT03036813)[7] Phase 3, multicenter, international, randomized, double-blind, parallel-group, placebo-controlled trial	• Males or females 12 to 65 years of age • Diagnosed with, or a confirmed medical history of HbSS, HbSC, HbSβ^0-thalassemia, HbSβ$^+$-thalassemia, or other SCD types ○ SCD genotype was detected by thin layer isoelectric focusing or HPLC with confirmatory DNA testing if required[56] • Experienced 1 to 10 VOCs[a] within the previous 12 months • Individuals taking hydroxyurea must be on a stable dose for ≥3 months prior to giving informed consent • Hb ≥5.5 to ≤10.5 g/dL during screening	• Individuals receiving chronic red blood cell transfusions, including for prophylactic purposes, or received a transfusion within the previous 60 days of enrollment • Erythropoietin within 28 days of enrollment[15] • Pregnant or breastfeeding patients[15] • VOC-related hospitalization occurred within the previous 14 days of providing informed consent • >10 VOCs within the previous 12 months that required a visit to a medical facility (eg, clinical, emergency room, hospital)[80] • Severe hepatic or renal dysfunction, defined as the following thresholds, respectively[80]: ○ ALT >4 times ULN ○ eGFR <30 mL/min/1.73 m^2 or on chronic dialysis
Safety and Efficacy of Voxelotor in Pediatric Patients with Sickle Cell Disease Aged 4 to 11 Years (HOPE-KIDS 1; NCT02850406)[b 55] Phase 2a, ongoing, multicenter, open-label, four-part, single- and multiple-dose study	• Males or females 4 to 11 years of age • Diagnosed with HbSS or HbSβ^0-thalassemia (diagnostic test not reported) • Children taking hydroxyurea must be on a stable dose for ≥3 months at enrollment, without any anticipation of dosage changes during the study period • Baseline Hb ≤10.5 g/dL	• Individuals receiving chronic red blood cell transfusions, including for prophylactic purposes, or received a transfusion within the previous 30 days • Within 14 days of giving informed consent, any prior hospitalization for VOC, dactylitis, splenic sequestration crisis, or ACS

[a] *The definition of a pain crises (similarly referred to as VOCs) varied slightly across applicable pivotal clinical trials:*

- *L-glutamine trial: Pain episode necessitating the utilization of parenterally administered narcotics or ketorolac within the confines of an emergency department, outpatient facility, or during inpatient hospitalization.*[50]
- *Crizanlizumab trial (SUSTAIN): Acute pain episodes due to vaso-occlusion that necessitates the utilization of oral or parenteral narcotics, or parenteral NSAIDs within a medical facility. Crises events also extended to incidences of ACS, splenic or hepatic sequestration, and priapism.*[49]
- *Voxelotor trial (HOPE): Acute pain episodes or ACS due to vaso-occlusion that necessitates the utilization of prescribed, or physician-directed use of oral or parental opioids, ketorolac, or other analgesics to alleviate moderate-to-severe pain within the confines of a health care setting (eg, emergency department, hospital, outpatient clinic).*[7, 57]

[b] *The HOPE-KIDS 1 trial is currently ongoing, with multiple phases (labeled A to D) that encompasses various age ranges and treatment regimens. Because interim results from phase C of the trial was used to help establish the basis for the accelerated approval of voxelotor in children aged 4 to 11 years, key eligibility criteria for part C of the trial are reported.*[51]

Abbreviations: ACS, acute chest syndrome; ALT, alanine aminotransferase; dL, deciliter; g, gram; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HIV, human immunodeficiency virus; INR, international normalized ratio; m, meter; min, minute; mg, milligram; SCD, sickle cell disease; ULN, upper limit of normal; VOCs, vaso-occlusive crises

APPENDIX E: RESULTS FROM THE L-GLUTAMINE, CRIZANLIZUMAB, AND VOXELOTOR PIVOTAL CLINICAL TRIALS

Table E1. Details of the L-glutamine, Crizanlizumab, and Voxelotor Pivotal Clinical Trials

Trial name Study identification number, RCT design	**Intervention and comparator** number of participants (n)	**Select efficacy and safety results**

A Phase 3 Trial of L-Glutamine in Sickle Cell Disease (NCT01179217)[54]
 	
Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial
	Intervention:
	• L-glutamine 0.3 g/kg PO twice daily (n=152)
	  ○ Max dose: 30 g daily
	Comparator:
	• Placebo PO twice daily (n=78)
		Efficacy results:
		Primary endpoint – number of pain crises over 48 weeks:
		• L-glutamine significantly reduced the number of pain crises compared to placebo (P=0.005) at week 48; 25% difference
		  ○ Median number of crises events:
		  ▪ 3 in the L-glutamine group
		  ▪ 4 in the placebo group
		Secondary endpoint(s):
		• L-glutamine significantly reduced the number of sickle cell pain-related hospitalizations (P=0.005) over 48 weeks; 33% difference
		  ○ Median number of hospitalizations:
		  ▪ 2 in the L-glutamine group
		  ▪ 3 in the placebo group
		• A statistically significant difference was not observed for L-glutamine vs. placebo for the number of non-hospitalized emergency department visits (P=0.09) or hematologic changes (ie, reticulocyte count, Hb and hematocrit values) from baseline to week 48
		Recurrent crises event time analysis:
		• L-glutamine reduced the average cumulative number of pain crises by 25% compared to placebo over the entire 48-week treatment period
		  ○ Intensity rate ratio: 0.75 (Andersen-Gill model 95% CI: 0.62–0.90; Lin-Wei-Yang-Ying modification of the Andersen-Gill model 95% CI: 0.55–1.01)
		• Compared to placebo, L-glutamine reduced the median time to first pain crises (HR: 0.69; 95% CI: 0.52–0.93; P=0.02) and second pain crises (HR: 0.68; 95% CI: 0.49–0.96; P=0.03)
		• L-glutamine recipients had significantly fewer ACS events compared to placebo recipients (8.6% vs. 23.1%, respectively; P=0.003) and fewer median cumulative days in the hospital (0–94 vs. 0–187; P=0.02)
		Subgroup analysis:
		• Male (RR: 0.73; 95% CI: 0.51–1.05) vs. females (RR: 0.81; 95% CI: 0.59–1.12): similar treatment effect based on sex (P=0.68)
		• ≤18 years of age (RR: 0.93; 95% CI: 0.67–1.29) vs. >18 years of age (RR: 0.64; 95% CI: 0.45–0.89): similar treatment effect based on age (P=0.12)
		• Concomitant hydroxyurea use (RR: 0.77; 95% CI: 0.58–1.03) vs. non-concomitant hydroxyurea use (RR: 0.78; 95% CI: 0.51–1.20): similar treatment effect based on hydroxyurea use (P=0.96)
		Safety results:
		• Numerically more AEs were reported in the placebo arm vs. L-glutamine arm (100% vs. 98%, respectively), including SAEs (87.1% vs. 78.2%)
		• AEs (≥5% difference from placebo): nausea, extremity (leg or arm) pain, back pain
		• Deaths: total n=2; both in the L-glutamine group died of sudden cardiac death
		  ○ Determined to be unrelated to the treatment by study investigators

[a] *The intention-to-treat (ITT) population included all participants who were randomized*[7, 53]

[b] *The per-protocol population included participants who were randomized, received ≥12 doses of crizanlizumab or placebo, and had no significant violations to the protocol*[53]

[c] *Defined as >1 g/dL increase in baseline Hb to week 24*[7, 55]

[d] *The per-protocol population included participants who completed 24 weeks of assigned treatment, and did not start hydroxyurea during the 24-week period, including after randomization*[7]

[e] *Adjusted for geographic region, hydroxyurea use, and age*[7]

[f] *The HOPE-KIDS 1 trial is currently ongoing, with multiple phases (labeled A to D) that encompasses various age ranges and treatment regimens. Because interim results from phase C of the trial were used to help establish the basis for the accelerated approval of voxelotor in children aged 4 to 11 years, select efficacy and safety results are reported*[55]

Abbreviations: ACS, acute chest syndrome; AEs, adverse events; CI, confidence interval; dL, deciliter; g, grams; Hb, hemoglobin; HR, hazard ratio; ITT, intention-to-treat; IV, intravenously; kg, kilogram; mg, milligram; NR, not reported; PO, orally; RR: rate ratio; SAE, serious adverse events; SCD, sickle cell disease; TEAE, treatment-emergent adverse event; VOC, vaso-occlusive crises

Table E1. Details of the L-glutamine, Crizanlizumab, and Voxelotor Pivotal Clinical Trials

Trial name Study identification number, RCT design	**Intervention and comparator** number of participants (n)	**Select efficacy and safety results**
		• Withdrawal due to AEs: L-glutamine (n=5); placebo (n=0) ○ Hypersplenism and abdominal pain (n=1); burning sensation in the feet (n=1); dyspepsia (n=1); hot flashes (n=1); pregnant (n=1) ○ Additionally, 2 pregnant women withdrew from the study, classified as "other"; although the pregnancy outcomes are unknown, no negative events were reported
Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease (SUSTAIN; NCT01895361)[53] Phase 2, randomized, double-blind, placebo-controlled trial	**Intervention:** • Crizanlizumab 2.5 mg/kg IV for 14 doses (low-dose; n=66) • Crizanlizumab 5 mg/kg IV for 14 doses (high-dose; n=67) **Comparator:** • Placebo IV for 14 doses (n=65) A total of 14 doses were administered IV over a 30-minute infusion during the treatment period: 2 loading doses were administered two weeks apart, followed by the maintenance dose every 4 weeks thereafter	**Efficacy results:** Primary endpoint (ITT population[a]) – median annual rate of sickle cell pain crises over 52 weeks: • Crizanlizumab 5 mg/kg (high-dose) vs. placebo: 1.63 vs. 2.98, respectively, representing a 45.3% reduction from placebo (P=0.01) • Crizanlizumab 2.5 mg/kg (low-dose) vs. placebo: 2.01 vs. 2.98, respectively, representing a 32.6% reduction from placebo; failed to reach statistical significance (P=0.18) Sensitivity analysis (per-protocol population[b]): • Crizanlizumab 5 mg/kg vs. placebo: 1.04 vs. 2.18, respectively, representing a 52.3% reduction from placebo (P=0.02) • Crizanlizumab 2.5 mg/kg vs. placebo: 2.00 vs. 2.18, respectively, representing a 8.3% reduction from placebo; failed to reach statistical significance (P=0.13) Subgroup analysis (ITT population[a]) of the primary endpoint: • History of crisis frequency (2 to 4, or 5 to 10): ○ 2 to 4 pain crises: ▪ Crizanlizumab 5 mg/kg vs. placebo: 1.14 vs. 2, respectively, representing a 43% reduction from placebo ▪ Crizanlizumab 2.5 mg/kg vs. placebo: 2 vs. 2, respectively, representing no difference from placebo ○ 5 to 10 pain crises: ▪ Crizanlizumab 5 mg/kg vs. placebo: 1.97 vs. 5.32, respectively, representing a 63% reduction from placebo ▪ Crizanlizumab 2.5 mg/kg vs. placebo: 3.02 vs. 5.32, respectively, representing a 43.2% reduction from placebo • Concomitant hydroxyurea use: ○ Among those taking concomitant hydroxyurea: ▪ Crizanlizumab 5 mg/kg vs. placebo: 2.43 vs. 3.58, respectively, representing a 32.1% reduction from placebo ▪ Crizanlizumab 2.5 mg/kg vs. placebo: 2 vs. 3.58, respectively, representing a 44.1% reduction from placebo ○ Among those **not** taking concomitant hydroxyurea ▪ Crizanlizumab 5 mg/kg vs. placebo: 1 vs. 2, respectively, representing a 50% reduction from placebo ▪ Crizanlizumab 2.5 mg/kg vs. placebo: 2.16 vs. 2, respectively, representing a 8% increase from placebo • SCD genotype: ○ Among those with HbSS: ▪ Crizanlizumab 5 mg/kg vs. placebo: 1.97 vs. 3.01, respectively, representing a 34.6% reduction from placebo ▪ Crizanlizumab 2.5 mg/kg vs. placebo: 2.05 vs. 3.01, respectively, representing a 31.9% reduction from placebo ○ Among those with other SCD types: ▪ Crizanlizumab 5 mg/kg vs. placebo: 0.99 vs. 2, respectively, representing a 50.5% reduction from placebo ▪ Crizanlizumab 2.5 mg/kg vs. placebo: 2 vs. 2, respectively, representing no difference from placebo

[a] *The intention-to-treat (ITT) population included all participants who were randomized*[7, 53]

[b] *The per-protocol population included participants who were randomized, received ≥12 doses of crizanlizumab or placebo, and had no significant violations to the protocol*[53]

[c] *Defined as >1 g/dL increase in baseline Hb to week 24*[7, 55]

[d] *The per-protocol population included participants who completed 24 weeks of assigned treatment, and did not start hydroxyurea during the 24-week period, including after randomization*[7]

[e] *Adjusted for geographic region, hydroxyurea use, and age*[7]

[f] *The HOPE-KIDS 1 trial is currently ongoing, with multiple phases (labeled A to D) that encompasses various age ranges and treatment regimens. Because interim results from phase C of the trial were used to help establish the basis for the accelerated approval of voxelotor in children aged 4 to 11 years, select efficacy and safety results are reported*[55]

Abbreviations: ACS, acute chest syndrome; AEs, adverse events; CI, confidence interval; dL, deciliter; g, grams; Hb, hemoglobin; HR, hazard ratio; ITT, intention-to-treat; IV, intravenously; kg, kilogram; mg, milligram; NR, not reported; PO, orally; RR: rate ratio; SAE, serious adverse events; SCD, sickle cell disease; TEAE, treatment-emergent adverse event; VOC, vaso-occlusive crises

Table E1. Details of the L-glutamine, Crizanlizumab, and Voxelotor Pivotal Clinical Trials

Trial name Study identification number, RCT design	**Intervention and comparator** number of participants (n)	**Select efficacy and safety results**
		Secondary endpoint(s): • Compared to placebo, crizanlizumab 5 mg/kg significantly increased the median time to first pain crisis (4.07 vs. 1.38, respectively; HR: 0.5; 95% CI: 0.33–0.74; P=0.001) and time to second pain crises (10.32 vs. 5.09, respectively; HR: 0.53; 95% CI: 0.33–0.87; P=0.02) • Crizanlizumab 5 mg/kg significantly reduced the annual rate of uncomplicated sickle cell pain crisis versus placebo (1.08 vs. 2.91, respectively), representing a 62.9% reduction from placebo (P=0.02) **Safety results:** • ≥1 AE: 86% crizanlizumab 5 mg/kg (57/66); 88% crizanlizumab 2.5 mg/kg (56/64); 89% placebo (55/62) • Most frequently reported AEs with crizanlizumab (≥5% difference from placebo in either active-treatment group): ○ Nausea, arthralgia, diarrhea • ≥1 SAE: 26% crizanlizumab 5 mg/kg (17/66); 33% crizanlizumab 2.5 mg/kg (21/64); 27% placebo (17/62) • Most frequently reported SAEs: ○ Pyrexia (crizanlizumab 5 mg/kg, n=2; crizanlizumab 2.5 mg/kg, n=0; placebo, n=1) ○ Influenza (crizanlizumab 5 mg/kg, n=0; crizanlizumab 2.5 mg/kg, n=3; placebo, n=0) ○ Pneumonia (crizanlizumab 5 mg/kg, n=3; crizanlizumab 2.5 mg/kg, n=2; placebo, n=3) • Deaths: total n=5; crizanlizumab 5 mg/kg (n=1, ACS; n=1, sepsis and endocarditis), crizanlizumab 2.5 mg/kg (n=1, ACS, respiratory failure, aspiration, and progressive vascular congestion), placebo (n=1, VOCs, coma, sepsis, ischemic stroke, and venous thrombosis; n=1, and right ventricular heart failure) ○ Determined to be unrelated to the treatment by study investigators • Single-occurrence AEs that were serious and potentially fatal, but did not cause death (n=3): ○ Sepsis (n=1; placebo group) ○ Anemia (n=1; crizanlizumab 2.5 mg/kg) ○ Intracranial hemorrhage (n=1; crizanlizumab 2.5 mg/kg)
A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease (HOPE; NCT03036813)[7,58] Phase 3, multicenter, international, randomized, double-blind, parallel-group, placebo-controlled trial	**Intervention:** • Voxelotor 1500 mg (n=90) PO once daily • Voxelotor 900 mg (n=92) PO once daily **Comparator:** • Placebo (n=92) PO once daily	**Efficacy results:** Primary endpoint (ITT population[a]) – Hb response[c] at week 24: • A significantly greater proportion of participants achieved a Hb response in the voxelotor 1500 mg group compared to placebo (51% vs. 7%; P<0.001) • Compared to placebo, a numerically greater proportion of participants achieved a Hb response with voxelotor 900 mg (33%); statistical significance not reported Sensitivity analysis (per-protocol population[d]) of the primary endpoint: • Voxelotor 1500 mg: 59%; voxelotor 900 mg: 38%; placebo: 9% Subgroup analysis (ITT population[a]) of the primary endpoint – difference in Hb response rates (voxelotor 1500 mg minus placebo): • History of VOC frequency: ○ 1 VOC: 55.2 (95% CI: 37.1–73.2) ○ 2 to 10 VOCs: 37.9 (95% CI: 22.8–53.0) • Concomitant hydroxyurea use: ○ Taking hydroxyurea at baseline: 50.0 (95% CI: 36.0–64.0)

[a] *The intention-to-treat (ITT) population included all participants who were randomized*[7, 53]

[b] *The per-protocol population included participants who were randomized, received ≥12 doses of crizanlizumab or placebo, and had no significant violations to the protocol*[53]

[c] *Defined as >1 g/dL increase in baseline Hb to week 24*[7, 55]

[d] *The per-protocol population included participants who completed 24 weeks of assigned treatment, and did not start hydroxyurea during the 24-week period, including after randomization*[7]

[e] *Adjusted for geographic region, hydroxyurea use, and age*[7]

[f] *The HOPE-KIDS 1 trial is currently ongoing, with multiple phases (labeled A to D) that encompasses various age ranges and treatment regimens. Because interim results from phase C of the trial were used to help establish the basis for the accelerated approval of voxelotor in children aged 4 to 11 years, select efficacy and safety results are reported*[55]

Abbreviations: ACS, acute chest syndrome; AEs, adverse events; CI, confidence interval; dL, deciliter; g, grams; Hb, hemoglobin; HR, hazard ratio; ITT, intention-to-treat; IV, intravenously; kg, kilogram; mg, milligram; NR, not reported; PO, orally; RR: rate ratio; SAE, serious adverse events; SCD, sickle cell disease; TEAE, treatment-emergent adverse event; VOC, vaso-occlusive crises

Table E1. Details of the L-glutamine, Crizanlizumab, and Voxelotor Pivotal Clinical Trials

Trial name Study identification number, RCT design	**Intervention and comparator** number of participants (n)	**Select efficacy and safety results**
		○ **Not** taking hydroxyurea at baseline: 34.9 (95% CI: 15.3–54.6) • Age: ○ 12 to <18 years of age: 51.3 (95% CI: 23.0–79.5) ○ ≥18 years of age: 43.3 (95% CI: 30.7–56.0) • Baseline anemia severity: ○ Hb <7 g/dL: 42.9 (95% CI: −2.0–87.8) ○ Hb ≥7 g/dL: 44.7 (95% CI: 32.7–56.6) Secondary endpoint(s) ITT population[a]: • A significantly greater adjusted mean change in hemoglobin from baseline to week 24 was observed with voxelotor 1500 mg (1.1 g/dL (95% CI: 0.9–1.4; P<0.001) ○ Voxelotor 900 mg: 0.6 g/dL (95% CI: 0.3–0.8) ○ Placebo: −0.1 g/dL (95% CI: −0.3–0.2) • Compared to placebo, voxelotor 1500 mg significantly improved select laboratory markers related to hemolysis from baseline to week 24 ○ Indirect bilirubin (mean change, −29.1% for voxelotor 1500 mg vs. −3.2% for placebo; P<0.001) ○ Relative change in the percentage of reticulocytes (mean decrease, −19.9% for voxelotor 1500 mg vs. mean increase, 4.5% for placebo; P<0.001) • Annualized adjusted[e] incidence rate of VOC (number of crises per person-year): ○ Voxelotor 1500 mg: 2.77 (95% CI: 2.15–3.57) ▪ Subgroup with ≥2 pain crises in the previous 12 months at baseline: 2.88 (95% CI: NR) ○ Voxelotor 900 mg: 2.76 (95% CI: 2.15–3.53) ▪ Subgroup with ≥2 pain crises in the previous 12 months at baseline: 3.39 (95% CI: NR) ○ Placebo: 3.19 (95% CI: 2.50–4.07) ▪ Subgroup with ≥2 pain crises in the previous 12 months at baseline: 3.50 (95% CI: NR) **Safety results:** • ≥1 TEAE: 94.3% voxelotor 1500 mg (83/88); 86% voxelotor 900 mg (86/92); 89% placebo (81/91) ○ Grade ≥3: 26.1% voxelotor 1500 mg (23/88); 22.8% voxelotor 900 mg (21/92); 26.4% placebo (24/91) • Most frequently reported AEs with voxelotor (≥5% difference from placebo in either active-treatment group): ○ Diarrhea, nausea, and abdominal pain • ≥1 SAE: 19.3% voxelotor 1500 mg (17/88); 17.4% voxelotor 900 mg (16/92); 16.5% placebo (15/91) ○ Treatment-related SAEs: 3.4% voxelotor 1500 mg (3/88); 3.3% voxelotor 900 mg (3/92); 1.1% placebo (1/91) • Deaths: total n=4; voxelotor 1500 mg (n=1, pulmonary sepsis, acute sickle hepatic crises, and sickle cell anemia with crisis); voxelotor 900 mg (n=1, sickle cell anemia with crisis); placebo (n=1, sickle cell anemia with crisis; n=1, cardiac arrest) ○ Determined to be unrelated to the treatment by study investigators • Withdrawal due to AEs: voxelotor 1500 mg (n=8); voxelotor 900 mg (n=5); placebo (n=4)

[a] *The intention-to-treat (ITT) population included all participants who were randomized*[7, 53]

[b] *The per-protocol population included participants who were randomized, received ≥12 doses of crizanlizumab or placebo, and had no significant violations to the protocol*[53]

[c] *Defined as >1 g/dL increase in baseline Hb to week 24*[7, 55]

[d] *The per-protocol population included participants who completed 24 weeks of assigned treatment, and did not start hydroxyurea during the 24-week period, including after randomization*[7]

[e] *Adjusted for geographic region, hydroxyurea use, and age*[7]

[f] *The HOPE-KIDS 1 trial is currently ongoing, with multiple phases (labeled A to D) that encompasses various age ranges and treatment regimens. Because interim results from phase C of the trial were used to help establish the basis for the accelerated approval of voxelotor in children aged 4 to 11 years, select efficacy and safety results are reported*[55]

Abbreviations: ACS, acute chest syndrome; AEs, adverse events; CI, confidence interval; dL, deciliter; g, grams; Hb, hemoglobin; HR, hazard ratio; ITT, intention-to-treat; IV, intravenously; kg, kilogram; mg, milligram; NR, not reported; PO, orally; RR: rate ratio; SAE, serious adverse events; SCD, sickle cell disease; TEAE, treatment-emergent adverse event; VOC, vaso-occlusive crises

Table E1. Details of the L-glutamine, Crizanlizumab, and Voxelotor Pivotal Clinical Trials

Trial name Study identification number, RCT design	**Intervention and comparator** number of participants (n)	**Select efficacy and safety results**
Safety and Efficacy of Voxelotor in Pediatric Patients with Sickle Cell Disease Aged 4 to 11 Years (HOPE-KIDS 1; NCT02850406)[f 55] Phase 2a, ongoing, multicenter, open-label, four-part, single- and multiple-dose study	**Intervention:** • Voxelotor weight-based dosing (n=45) ○ 10 to <20 kg: 600 mg once daily ○ 20 to <40 kg: 900 mg once daily ○ ≥40 kg: 1500 mg once daily **Comparator:** none	**Interim efficacy results (Phase C; children aged 4 to 11 years):** • 47% of participants achieved a Hb response[c] at week 24 (n=34) ○ >1.5 g/dL increase in Hb from baseline to week 24: 35% ○ >2.0 g/dL increase in Hb from baseline to week 24: 21% ○ Any magnitude of increase in Hb from baseline to week 24: 82% • From baseline to week 24, the mean Hb change was 1 g/dL • Voxelotor improved hemolysis-associated laboratory markers, as measured by the mean percent change from baseline at week 24 ○ Indirect bilirubin: −38.6% (range −76.0% to 40.0%; n=28) ○ Reticulocyte count: −3.3% (range −95.0% to 110.3%; n=31) ○ Lactate dehydrogenase: −2.6% (range −36.6% to 44.2%; n=32) **Interim safety results (Phase C; children aged 4 to 11 years):** • Most frequently reported non-SCD-related TEAEs (≥10% of participants): pyrexia, rash, vomiting, diarrhea, abdominal pain, headache, extremity pain, viral infection, and upper respiratory tract infection • Any drug-related TEAE: 49% (22/45) ○ Most frequently reported drug-related TEAEs (≥5% of participants): rash, diarrhea, vomiting, abdominal pain, and elevations in transaminases ▪ The majority were classified as grade 1 • Temporary dose reductions of voxelotor due to drug-related TEAEs occurred in a total of 4 participants: rash (n=1); hypersensitivity (n=1; ultimately discontinued voxelotor due to allergic edema, sickle cell anemia with crisis, and pyrexia); elevations in liver enzymes (n=1); elevations in liver enzymes and bilirubin (n=1) • Deaths: n=0 • Withdrawal due to an AE: n=3

[a] The intention-to-treat (ITT) population included all participants who were randomized[7, 53]

[b] The per-protocol population included participants who were randomized, received ≥12 doses of crizanlizumab or placebo, and had no significant violations to the protocol[53]

[c] Defined as >1 g/dL increase in baseline Hb to week 24[7, 55]

[d] The per-protocol population included participants who completed 24 weeks of assigned treatment, and did not start hydroxyurea during the 24-week period, including after randomization[7]

[e] Adjusted for geographic region, hydroxyurea use, and age[7]

[f] The HOPE-KIDS 1 trial is currently ongoing, with multiple phases (labeled A to D) that encompasses various age ranges and treatment regimens. Because interim results from phase C of the trial were used to help establish the basis for the accelerated approval of voxelotor in children aged 4 to 11 years, select efficacy and safety results are reported[55]

Abbreviations: ACS, acute chest syndrome; AEs, adverse events; CI, confidence interval; dL, deciliter; g, grams; Hb, hemoglobin; HR, hazard ratio; ITT, intention-to-treat; IV, intravenously; kg, kilogram; mg, milligram; NR, not reported; PO, orally; RR: rate ratio; SAE, serious adverse events; SCD, sickle cell disease; TEAE, treatment-emergent adverse event; VOC, vaso-occlusive crises

APPENDIX F: UTAH MEDICAID PRIOR AUTHORIZATION REQUEST FORM

Rare Disease Medications

Member and Medication Information * indicates required field	
*Member ID:	*Member Name:
*DOB:	*Weight:
*Medication Name/Strength:	□ Do Not Substitute. Authorizations will be processed for the preferred Generic/Brand equivalent unless specified.
*Directions for use:	
Provider Information * indicates required field	
*Requesting Provider Name:	*NPI:
*Address:	
*Contact Person:	*Phone #:
*Fax #:	Email:
Medically Billed Information * indicates required field for all medically billed products	
*Diagnosis Code:	*HCPCS Code:
*Dosing Frequency:	*HCPCS Units per dose:
Servicing Provider Name:	NPI:
Servicing Provider Address:	
Facility/Clinic Name:	NPI:
Facility/Clinic Address:	
Fax form and relevant documentation including: laboratory results, chart notes and/or updated provider letter to Pharmacy PA at **855-828-4992,** to prevent processing delays.	

Criteria for Approval (all criteria must be met and documented in submitted chart notes):

□ Medication is prescribed by or in consultation with a physician who specializes in the disease treatment.

- Specialist name and credentials:_____

□ Documented diagnosis:_____ Chart note page #:_____

- Genetic testing, if applicable. Chart note page #:_____
- Other confirmation testing, if applicable. Chart note page #:_____

□ Include latest treatment guidelines or compendia treatment recommendations, if applicable, with request.

□ Use must follow FDA-approved labeling *(including monitoring for boxed warnings and contraindications)*.

- Applicable monitoring for boxed warnings. Chart note page #:_____

□ If current treatment standards recommend other treatment modalities or interventions prior to use of the requested drug, document the use of appropriate first line treatments or interventions.

- Treatment/Interventions:_____ Chart note page #:_____

□ Off Label or Compendia Use Additional Criteria: Requests for any off-label indications must be supported by at least one (1) major multi-site study or three (3) smaller studies published in JAMA, NEJM, Lancet or other peer review specialty medical journals within the most recent five (5) years. Supporting documentation must be included. Compendia use must be recommended by generally accepted compendia such as American Hospital Formulary Service Drug Information (AHFS), United States Pharmacopeia-Drug Information (USP-DI), the DRUGDEX Information System, and the peer-reviewed medical literature.

□ Additional drug-specific criteria may apply and may guide adjudication; additional information may be needed. See addendum for details, page 2.

Re-authorization Criteria: if applicable:
Updated letter of medical necessity or updated chart notes demonstrating positive clinical response

Initial Authorization: Up to six (6) months, if applicable
Reauthorization: Up to one (1) year, if applicable

Note:

❖ Use appropriate HCPCS code for billing if applicable
Coverage and Reimbursement code look up:
https://health.utah.gov/stplan/lookup/CoverageLookup.php
HCPCS NDC Crosswalk: https://health.utah.gov/stplan/lookup/FeeScheduleDownload.php

PROVIDER CERTIFICATION

I hereby certify this treatment is indicated, necessary and meets the guidelines for use.

_____ _____

Prescriber's Signature Date

Brand (generic)	**Additional Criteria**
Luxturna (voretigene)	What is the patient's diagnosis: □ Biallelic RPE65 mutation-associated retinal dystrophy □ Other, please specify:____ Which eye is being treated: □ Left eye □ Right eye □ Both eyes *If BOTH eyes, do you agree that the initial eye's injection and the second eye's injection will be administered at least 6 days apart? □ Yes □ No Has the patient received Luxturna previously? □ Yes □ No *If yes, which eye(s) were previously treated? □ Left eye □ Right eye

	*If treating the additional eye, do you agree that the initial eye's injection and the second eye's injection will be administered at least 6 days apart? □ Yes □ No Documented diagnosis of biallelic RPE65 mutation-associated retinal dystrophy confirmed by genetic testing? (please include genetic testing results) □ Yes □ No Authorization: once per lifetime
Zolgensma	Authorization: once per lifetime

APPENDIX G: CONSIDERATIONS FOR PRIOR AUTHORIZATION (PA) CRITERIA

The Drug Utilization and Review (DUR) board may consider implementing the following drug-specific PA criteria for L-glutamine, voxelotor, and crizanlizumab.

1. *Restrict based on the labeled age for the indication*
    a. L-glutamine is indicated for ages ≥5 years to decrease sickle cell disease (SCD)-related acute complications.[14]
    b. Voxelotor is indicated for ages ≥4 years for the treatment of SCD.[15]
    c. Crizanlizumab is indicated for ages ≥16 years to decrease the frequency of VOCs.[17]
2. *Consider having the medication be prescribed by or in consultation with a hematologist or SCD specialist*
    a. Because SCD is a rare condition,[3] patients should be treated by or in consultation with a provider specialized in managing SCD.
3. *Require provider attestation for the diagnosis of SCD and may consider requiring documentation of the hemoglobin genotype*
    a. A patient's sickle cell status (SCD or sickle cell trait [SCT]) is diagnosed by a complete blood count with mean corpuscular volume, **and** hemoglobin (Hb) electrophoresis, high performance liquid chromatography (HPLC), or genetic testing, among other tests (eg, isoelectric focusing, polymerase chain reaction-based techniques).[31,36,42]
        i. The laboratory tests for Hb analysis varied across the pivotal clinical trials but consisted of Hb electrophoresis,[54] HPLC,[56,57] or thin layer isoelectric focusing with confirmatory genetic testing if needed.[56]
        ii. Note that diagnostic tests may have limitations regarding which Hb variants they can identify.[36]
        iii. L-glutamine, voxelotor, and crizanlizumab are indicated for all SCD genotypes.[14,15,17] Unlike pivotal trials for voxelotor (HOPE) and crizanlizumab (SUSTAIN) that included patients with all SCD genotypes,[7,53] the pivotal trial for L-glutamine only included patients with genotypes HbSS or HbSβ^0-thalassemia.[54] Nonetheless, the FDA indication for L-glutamine does not restrict its use based on genotype,[14] and expert opinion guidance suggests L-glutamine as an add-on option for patients with SCD in general and persistent vaso-occlusive crises (VOCs) despite hydroxyurea monotherapy.[66]
4. *Documentation (or provider attestation) showing that treatment-naïve patients or those taking hydroxyurea monotherapy have experienced at least one sickle cell pain crisis in the previous 12 months*
    a. In the L-glutamine, HOPE, and SUSTAIN pivotal clinical trials, participants were required to experience ≥1 (HOPE) or ≥2 (SUSTAIN and L-glutamine RCT) sickle cell pain crises, also referred VOCs, within the previous year.[7,53,54]
        i. SUSTAIN and HOPE had an upper threshold of 10 VOCs,[7,53] whereas the L-glutamine RCT had no upper limit.[54]

Additional considerations:

5. *Whether to step-through hydroxyurea before initiating newer disease-modifying agents:*
    a. Patients were not required to first fail hydroxyurea in order to enter the pivotal studies of these newer agents.[7,53-55] Of the patients enrolled into the studies who were treated with combination therapy (hydroxyurea + study drug), it is unclear what proportion had prior failure with hydroxyurea. There are no head-to-head RCTs of hydroxyurea vs. any of the newer agents.
        i. If a requirement is made to step through hydroxyurea, a longtime standard of care for SCA, before receiving a newer agent,[31,65] consider including the opportunity for the provider to express rationale for cases where it would be inappropriate to employ hydroxyurea first (eg, contraindications, drug interactions, lack of evidence for use in certain SCD genotypes).
6. *Consider allowing the use of newer agents with or without hydroxyurea*
    a. Although hydroxyurea is considered the standard of care along with other disease-modifying therapies,[45] it may not be sufficient as monotherapy for all patients. Across the reviewed pivotal clinical trials, at least two-thirds of enrolled participants had residual VOCs despite hydroxyurea monotherapy use prior to enrollment and were allowed to continue hydroxyurea as background treatment while on the experimental drug.[7,53-55]
    b. Some patients may be more hesitant to adhere to hydroxyurea than the newer agents because of side effects they have heard of that are associated with chemotherapeutic doses (eg, teratogenicity, malignancy).[47] To mitigate concerns, patients should be counseled about the lower dosing of hydroxyurea for SCD relative to chemotherapy and differences in expected side effects to help encourage consistent adherence.[47]
    c. L-glutamine, voxelotor, and crizanlizumab may be used as alternative options for patients who are unresponsive or intolerant to hydroxyurea, or as additive therapy for patients with residual symptoms while taking hydroxyurea.[64,66]
        i. L-glutamine and crizanlizumab may be especially beneficial for patients who continue to have persistent VOCs with or without hydroxyurea.[66] In both pivotal RCTs, L-glutamine and crizanlizumab (at the FDA approved dosage of 5 mg/kg) significantly reduced the occurrence of sickle cell pain crises compared to placebo.[53,54]
        ii. Voxelotor, in combination with or without hydroxyurea, may be especially beneficial for patients with persistent anemia.[47,64] Compared to placebo, voxelotor demonstrated a significant improvement in Hb levels from baseline to week 24 in the HOPE trial.[7]
7. *Whether concomitant use of newer disease-modifying agents should be employed:*
    a. Currently there are no clinical trials assessing the combined use of L-glutamine, voxelotor, and crizanlizumab.[25,64,66] Because each of these agents targets a different underlying pathophysiological mechanism of SCD,[64] combination use may theoretically be beneficial.[66] Nonetheless, uncertainty exists regarding the optimal approach for combing these agents and whether the potential benefits will outweigh the risks.[26]
8. *May consider requiring attestation that the prescriber has checked the patient's Hb concentration before starting* ***voxelotor***
    a. For the pivotal studies of voxelotor (HOPE and HOPE-KIDS), participants were required to have a baseline Hb concentration of ≤10.5 g/dL.[7,55] Hb response was evaluated as the primary outcome for voxelotor,[7] rather than VOC rate which was the primary outcome for L-glutamine and

crizanlizumab.[53,54] Voxelotor treatment increased Hb modestly (1.1 g/dL in the 1,500 mg dosage group).[7]

9. *Crizanlizumab should be prepared and administered by a healthcare provider in a health care setting.*[17]