MarketVue®

Sickle Cell Disease (U.S.)

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REACH Market Research

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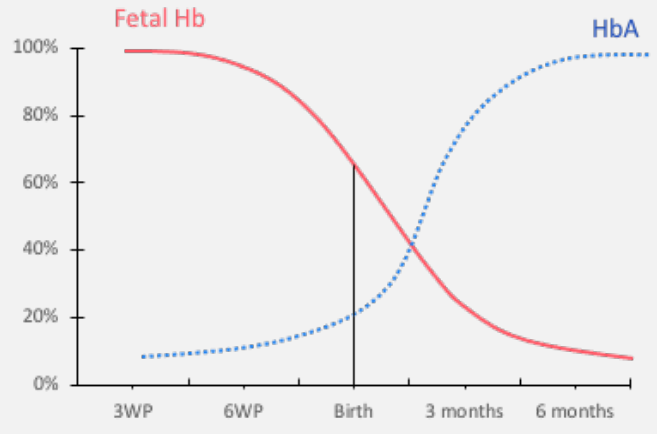
1. DISEASE OVERVIEW

A chronic and progressive inherited genetic disorder

Sickle cell disease (SCD) is an inherited genetic disorder that affects red blood cell (RBC) shape, function, and lifespan. The underlying cause of the disease is a single mutation in the hemoglobin gene (*HBB)* that leads to the production of abnormal hemoglobin (HbS). HbS carries less oxygen than normal hemoglobin and forms long polymers that cause RBCs to misshapen. These deformed RBCs stick together, block blood flow to major organs, and carry less oxygen than healthy RBCs. As a result, SCD patients experience chronic oxygen depravation of end organs that only worsens with time causing organ failure and death. In addition, these patients live in chronic pain, with sporadic episodes of severe, debilitating pain attacks among other complications (e.g., infection, anemia).

Abnormal hemoglobin is at the center of SCD disease pathology. Fetal hemoglobin (HbF) is the major hemoglobin present before birth and accounts for 60-80% of total hemoglobin at birth. In individuals without SCD, HbF is almost entirely replaced by adult hemoglobin (HbA) between 6-12 months of age (Figure 1.1). In SCD adults, HbF is replaced by abnormal HbS although some patients maintain slightly higher HbF levels than healthy adults. However, research has shown that increased HbF in SCD patients improves the clinical features of the disease. Today, increasing HbF in SCD patients is a key focus for drug developers.

Figure 1.1 Hemoglobin switching



HbF plays a protective role in SCD.

- The protective role of HbF in SCD was first evidenced by the observation that SCD infants are asymptomatic until after 6 months of age when HbF levels fall off.
- SCD patients with higher levels of HbF have mild disease compared to those with lower HbF levels.
- In animal studies, reactivating HbF production in adults effectively reverses SCD.

> *"We have known for many, many years that high levels of fetal hemoglobin have an important clinical benefit in sickle cell patients. Now our challenge is to see if we can capitalize on this knowledge to the benefit of patients. There are at least 12 different ways that levels of fetal hemoglobin expression are regulated. Can we exploit them to increase its production in children and adults with sickle cell disease? I sure hope so."* ***- U.S. Hematologist***

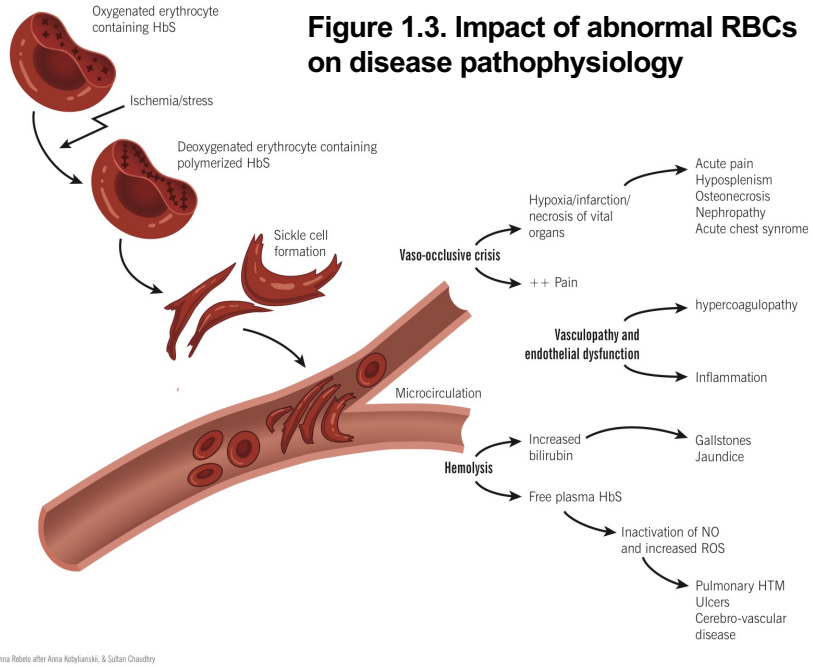
Figure 1.2 Key features of SCD

Sickled-shaped RBCs cause pain, anemia, multi-organ complications, and irreversible end organ damage.	**SCD red blood cell morphology** • Sticky – SCD RBCs stick to each other and to the endothelium thereby blocking blood flow and causing low oxygen delivery to major organs (e.g., spleen, kidneys, brain, lungs); this vascular occlusion leads to tissue death and irreversible organ damage. Vascular occlusion also causes chronic and severe acute pain events. • Sickle shaped and stiff – the misshapen morphology of SCD RBCs is caused by polymerization of HbS and contributes to occlusion of the microvasculature. • Fragile – cells break apart easily and only live 10-20 days compared to 120 days for healthy RBCs. As a result, patients face chronic low RBC counts (anemia).
SCD is chronic, progressive, and life-threatening with symptom onset at ~6 months of age.	• **Chronic** – By age one, HbS is the predominant form hemoglobin in SCD patients. From then, patients face a constellation of complications resulting from poor functioning RBCs and subsequent chronic organ impairment. • **Progressive** – the chronic oxygen depravation of end organs begins years before overt symptoms appear. As patients age, organ function worsens and ultimately leads to organ failure and even death. • **Life threatening** – The median age of death for a SCD patient is 43 years old[1]. Acute organ failure, acute chest syndrome, and infection are the leading causes of death in SCD patients.[2]

Pain is a hallmark of SCD

- Patients experience chronic daily pain with intermittent bouts of severe, acute pain events called vaso-occlusive crises (VOCs).
- VOCs are a common, spontaneous, painful, and debilitating complication of SCD. The pain is so severe that it leads patients to seek emergency medical care and physicians to hospitalize patients. The pain results from sticky, misshaped RBCs blocking blood flow through tiny blood vessels in the chest, abdomen, and joints.
- Hemolysis of RBCs leads to anemia where patients have low RBC counts and cannot supply adequate oxygen levels to the body's organs.

Figure 1.3. Impact of abnormal RBCs on disease pathophysiology



1. Payne AB, et al. Trends in Sickle Cell Disease-Related Mortality in the United States, 1979 to 2017. Ann Emerg Med. 2020 Sep;76(3S):S28-S36.
2. Lanzkron S, Carroll CP, Haywood C Jr. Mortality rates and age at death from sickle cell disease: U.S., 1979-2005. Public Health Rep. 2013 Mar-Apr;128(2):110-6.

2. EPIDEMIOLOGY & PATIENT POPULATIONS

United States

DIAGNOSED PREVALENCE & DRUG-TREATED PATIENTS

89,000[1]	99%	56%[2]	49,148
Disease prevalence	of patients are diagnosed	of patients receive treatment	patients receiving treatment

KEY POPULATION DYNAMICS

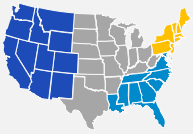
Diagnosis. Nearly all SCD patients are diagnosed at birth thanks to state-based newborn screening programs in all 50 states.

Subtypes. There are seven subtypes of SCD; two account for most patients. HbSS is the most severe and most prevalent form of the disease; patients carry two mutated *HBB* genes. HbSC patients carry one abnormal and one healthy *HBB* gene and have a mild form of SCD. Other forms of SCD including HbS beta thalassemia, HbSD, HbSE, an HbSO.

SCD Subtype[3]	% of SCD Patients
HbSS	75%
HbSC	18%

Patient phenotypes. The SCD population can be segmented by Hb levels or by the frequency of annual VOCs (pain crises). The predominant patient phenotype – low Hb level or pain crises – is a key determinant in treatment selection (Figure 2.1 and 2.2).

Geographic distribution. 85% of SCD patients live in 18 states:[4]



- **Northeast:** NY, NJ, PA
- **Central:** TX, MI, IL, OH
- **South**: FL, GA, NC, SC, AL, TN, VA, MS, LA, MA
- **West**: CA

1. See Section 7 on methodology
2. REACH primary market research; see Section 7 on methodology
3. Saraf SL, Molokie RE, Nouraie M, et al. Differences in the clinical and genotypic presentation of sickle cell disease around the world. Paediatr Respir Rev. 2014;15(1):4-12.
4. Wilson-Frederick SM, Hulihan M, Anderson KK. Prevalence of Sickle Cell Disease among Medicaid Beneficiaries in 2012. CMS Office of Minority Health Data Highlight, No. 16. Baltimore, MD. 2019.

Distinct phenotypes demarcate two market-relevant subpopulations

A patient's predominant phenotype (high frequency of VOCs versus low hemoglobin levels) has added a key decision point in the treatment algorithm for SCD. This change is driven by the recent availability of Novartis's Adakveo (crizanlizumab) and Global Blood Therapeutics' Oxbryta (voxelotor) (see Section 5, Emerging Therapies). Adakveo has shown its effectiveness at reducing VOCs while Oxbryta has demonstrated efficacy for increasing hemoglobin levels in SCD patients. The availability of Adakveo and Oxbryta not only give physicians much needed treatment options, but they have also split the market into two segments based on the predominant patient phenotype.

The clinical manifestations of SCD occur along a spectrum. The frequency of VOCs is a clinical manifestation that is highly variable with nearly one-third of patients being VOC-free or having only one crisis a year. Indeed, surveyed U.S. hematologists (adult and pediatric) report that the largest share (40%) of their SCD patients have two to five VOCs a year. With regards to how the SCD patient population segments based on hemoglobin levels, patients are evenly split between having hemoglobin levels that are in the range of 8.5-10.5g/dL and less than 8.5g/dL.

Figure 2.1. SCD population segmented by annual VOC frequency[1]

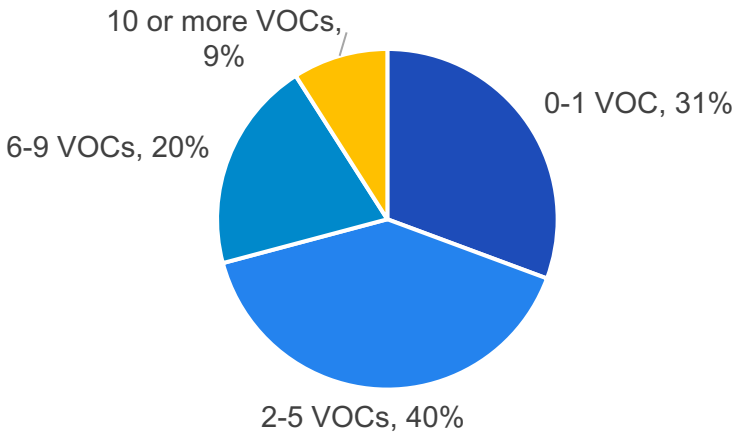
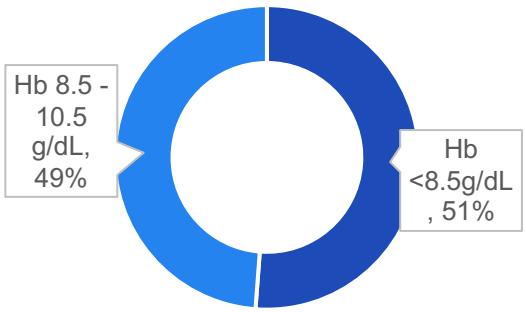


Table 2.1. Hb levels in healthy and SCD adults[2]

Patient type	Hb level
Health adult, male	13.8-17.2 g/dL
Healthy adult, female	12.1 to 15.1 g/dL
SCD, HbSS	8.5 g/dL (mean)
SCD, HbSC	11 g/dL (mean)

Figure 2.2. SCD population segmented by Hb levels[1]



1. REACH primary market research; see Section 7 on methodology
2. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. *N Engl J Med.* 2017;376(16):1561-1573.

3. CURRENT TREATMENT

Overview

Current treatment of SCD is focused on managing a constellation of symptoms and complications that arise as a result of poor RBC health and poor blood flow to and oxygenation of major organs. Treatment is primarily focused on managing chronic and acute pain – the most reported symptom of SCD – and chronic anemia. Of note, SCD can be cured with an allogeneic bone marrow transplant; however, only 5% of patients receive this intervention (Figure 3.1). Instead, most physicians rely on a handful of drugs and regular blood transfusions to manage the disease and its complications while patients turn to diet, lifestyle changes, and over-the-counter pain medications to improve daily living.

Disease management and treatment goals

Manage and reduce acute pain crises. Disease management in SCD is focused on managing acute crises in the hospital with hydration therapy, oxygen therapy, RBC transfusions, and/or opioids. Physicians also try to prevent VOCs from happening using hydroxyurea and Adakveo.

Manage chronic pain. SCD patients can be in pain as much as 55% of the time[1] which disrupts daily living (e.g., working, attending school, socializing). Chronic pain is managed at home with over-the-counter analgesics and prescription pain medications.

Prevent and treat infections. The risk of infection in SCD patients is high owing to poor functioning of their spleen – an important immune system organ that fights infection. Penicillin prophylaxis is commonly used to prevent infections.

Manage chronic hemolytic anemia. Sickled RBCs are fragile; they break apart easily and die much faster than normal RBCs. Hence, patients have too few RBCs (anemia) leading to fatigue and chronic low oxygen levels in major organs that causes irreversible end organ damage.

Prevent stokes. Nearly 1 in 4 SCD patients have a stroke by the age of 45[2]. While blood transfusions can decrease the risk of stroke, their utility is limited due to alloimmunization and iron overload.

> *"With SCD the longer you have it then the more likely you'll have a complication. Drugs we have are disease modifiers, but they don't eliminate the complications and issues. Around age 12 to 18 is where patients start to have a lot of issues with their disease"*
>
> – **U.S. Adult Hematologist**

1. Chakravorty S, et al. Patient-reported experience measure in sickle cell disease. Arch Dis Child. 2018 Dec;103(12):1104-1109.
2. Verduzco LA, Nathan DG. Sickle cell disease and stroke. Blood. 2009 Dec 10;114(25):5117-25.

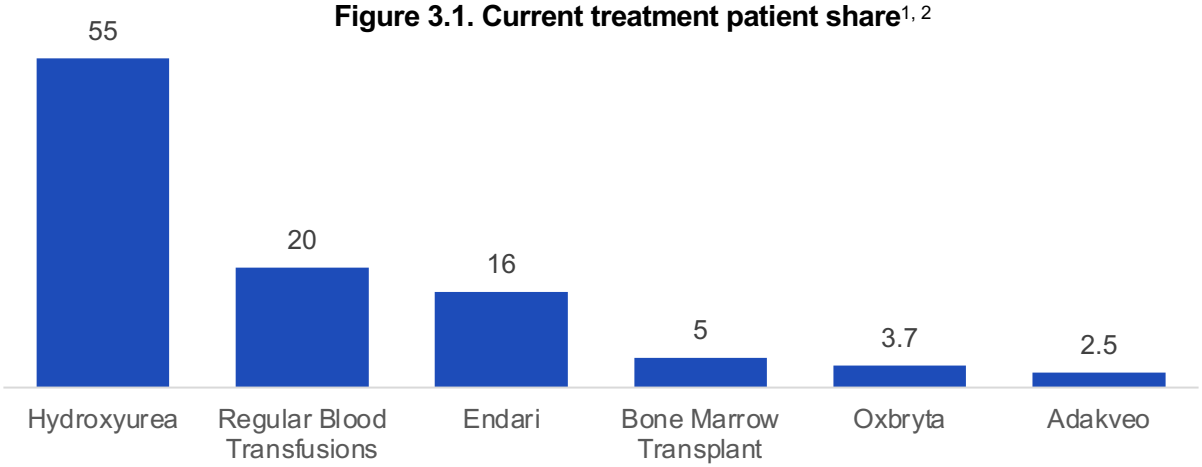
New market entrants offer much needed expansion of treatment options

Treatment options for SCD include four drugs and two types of cell therapy. Prior to 2018, hydroxyurea was the only available drug treatment but 2017 and 2019 brought three new therapies to the market – Endari, Adakveo, and Oxbryta.

Table 3.1. There are six treatment options for SCD.

Treatment (*Company*)	Formulation and Dosing	FDA Approval Year	Age of Use	Effect on Disease
Small Molecules				
Hydroxyurea (multiple generics)	Oral capsule, QD	1998	2+	Increases HbF, reduces VOCs
Endari (L-glutamine) *Emmaus Medical*	Oral powder, BID	2017	5+	Unclear; reduces acute complications of SCD
Oxbryta (voxelotor) *Global Blood Therapeutics*	Oral tablet (3 tablets), QD	2019	12+	Increase Hb levels by 1g/dL
Biologics				
Adakveo (crizanlizumab) *Novartis*	IV monthly after initial and loading doses	2019	16+	Reduces VOCs by 45.3%
Cell Therapies				
Regular blood transfusion	IV	n/a	n/a	Healthy RBCs lessen anemia, reduce blood viscosity
Bone marrow transplant	IV	n/a	n/a	Increases healthy RBCs; SCD cure

Figure 3.1. Current treatment patient share[1, 2]



1. REACH primary market research; see Section 7 on methodology
2. Secure-SCD Registry, Surveillance Epidemiology of Coronavirus (COVID-19) https://covidsicklecell.org, The Medical College of Wisconsin.

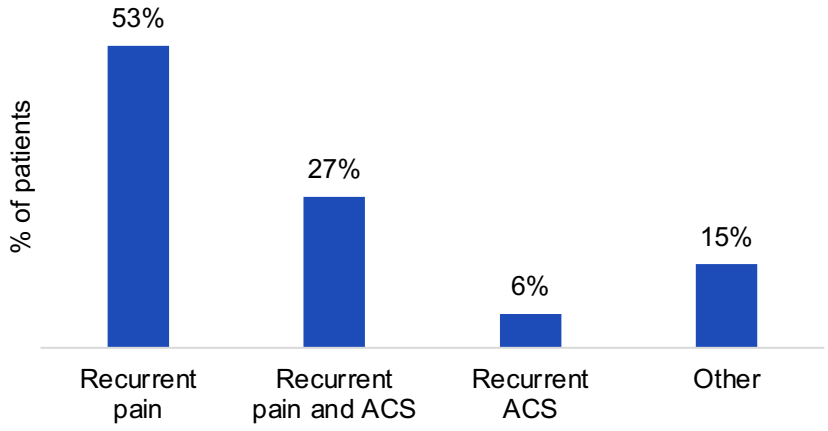
Standard of care: Hydroxyurea, a chemotherapy repurposed for SCD

Hydroxyurea is a very safe and effective treatment that has been prescribed to SCD patients for nearly 25 years; until 2018 it was the only drug treatment option. As the standard of care for SCD, hydroxyurea is first-line therapy for children (age 2+) and adults with recurrent moderate to severe painful crises. Moreover, its first-line use is reinforced by the fact that commercial payers and Medicaid require hydroxyurea step therapy before paying for other drug options (Figure 6.1).

Hydroxyurea is generally prescribed to help patients manage and prevent recurrent pain and acute chest syndrome (Figure 3.2).

Approximately half (55%) of SCD patients take hydroxyurea. Its use is held back in part because a subset of providers and patients fear that the drug could cause cancer. For example, two separate studies report that 27% of pediatric providers[1] and 40% of adult providers[2] state that fear of cancer has interfered with their use of hydroxyurea.

Figure 3.2. Reasons for hydroxyurea use[3]



Key attributes of hydroxyurea

- Daily, oral capsule
- Hydroxyurea is administered as monotherapy.
- Requires monitoring of patient's blood count every two weeks to check for cytopenia which is reversible once hydroxyurea is stopped.
- Approved use in the broadest age group (2 years or older) of all SCD treatments.
- Acts by increasing HbF which in turn reduces the frequency of pain crises and reduces the need for blood transfusions.
- Hydroxyurea is generally required to be a step therapy by commercial and government (Medicaid and Medicare) payers ahead of Adakveo or Oxbryta for prescription reimbursement (Table 6.2).
- The drug is proven effective in HbSS or HbSβ^0 thalassemia.

"Hydroxyurea is our standard of care and it's a great drug. Almost all patients should be taking it, but they aren't. It's cheap. It works. That's clearly not enough. Compliance is a big issue. It's a shame because it is really an ideal drug."

– U.S. Adult Hematologist

"We've had hydroxyurea for a long time. It's the best thing we have and it's been remarkably underutilized even in our practice. It's a safe drug, it needs a moderate amount of monitoring, side effects are tolerable, and it prevents somewhere around probably half of pain episodes, acute chest, and maybe has some benefits in delaying end organ damage, long-term morbidity, and even mortality."

– U.S. Adult Hematologist

1. Brandow AM. et al. **Hydroxyurea in children with sickle cell disease: practice patterns and barriers to utilization.** Am J Hematol. 2010 Aug;85(8):611-3.
2. Zumberg MS. et al. Hydroxyurea therapy for sickle cell disease in community-based practices: a survey of Florida and North Carolina hematologists/oncologists. Am J Hematol. 2005 Jun;79(2):107-13.
3. REACH primary market research; see Section 7 on methodology

Novartis' Adakveo has a clear value proposition for treating VOCs

- Adakveo is a anti-P-selectin monoclonal antibody that reduces the frequency of VOCs in adult and pediatric SCD patients (age 16 and older). Phase 3 data show that the drug reduces VOCs by 45.3%[1]. It is given as a monthly infusion following an initial dose and loading dose within the first two weeks of treatment.
- There is a clear consensus among surveyed hematologists that Adakveo's ability to reduce the number of VOCs in SCD patients is the drug's single greatest advantage. These data combined with the drug's label for use to reduce VOCs and physician preferences to use the drug in patients with recurrent and refractory VOCs create a clear path for Adakveo's use.

Figure 3.3. ADAKVEO advantages[2]

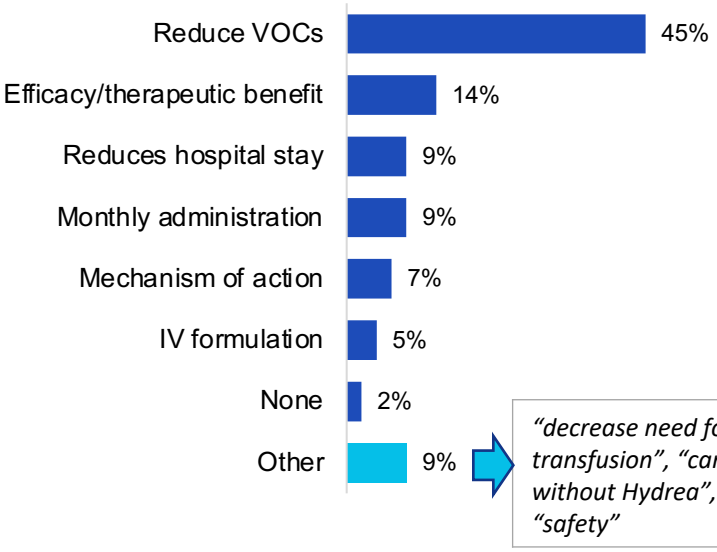
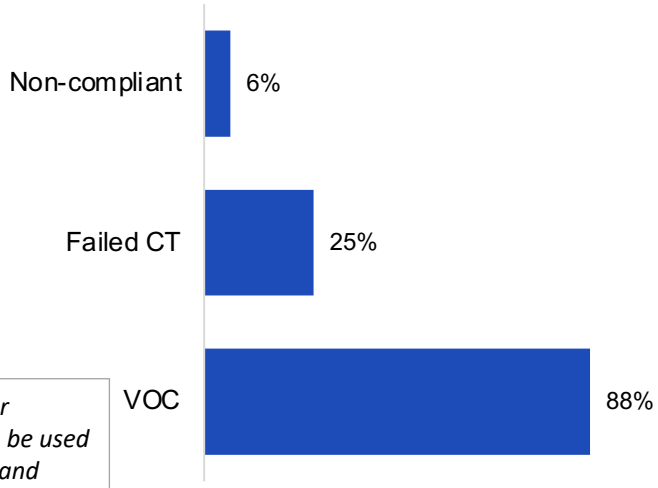


Figure 3.4. Types of patients being treated with Adakveo[2]



Hematologists' insights on the advantages of Adakveo (each quote is from a different physician).

"Can use regardless of Hgb level and compliance is 100% if they come to their appointments."

"It can reduce the incidence of VOC and pain crises therefore potentially lessening hospitalization stays."

"Different therapeutic approach with minimizing inflammation. IV administration. Has some positives and some negatives."

"It is a P-selectin targeting antibody that appears to be extremely effective at reducing the incidence of sickle cell disease-related morbidity such as pain crises and VOCs, with acceptable safety signals."

1. Ataga KI et al.. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med. 2017 Feb 2;376(5):429-439.
2. REACH primary market research; see Section 7 on methodology

GBT'S Oxbryta is garnering broad use

- Oxbryta is a hemoglobin oxygen-affinity modulator that reduces polymerization of HbS, increases RBC hemoglobin levels, and decreases indicators of hemolysis. It is given orally, once-daily (taken as three tablets).
- Among those hematologists that are aware of Oxbryta, there is no consensus on what they consider to be the drug's advantage. Instead, physicians share a range advantages that align with the product's label and marketed benefits including its ability to increase hemoglobin levels by as much as 1g/dL and its oral formulation. Interestingly, nearly one-quarter of these hematologists site that the drug reduces VOCs for which the drug is not labeled.
- Hematologists' use of Oxbryta by patient type mirrors their perceptions of the drug's advantages – use in transfusion-dependent patients, patients with low Hb levels less than 10 g/dL, patients who have failed hydroxyurea, and those with frequent VOCs. Importantly, a patient's level of motivation and demonstrated ability to be compliant with treatment is an important factor that 1 in 4 hematologists say is a characteristic of patients to whom they have prescribed Oxbryta.

Figure 3.5. Advantages of Oxbryta[1]

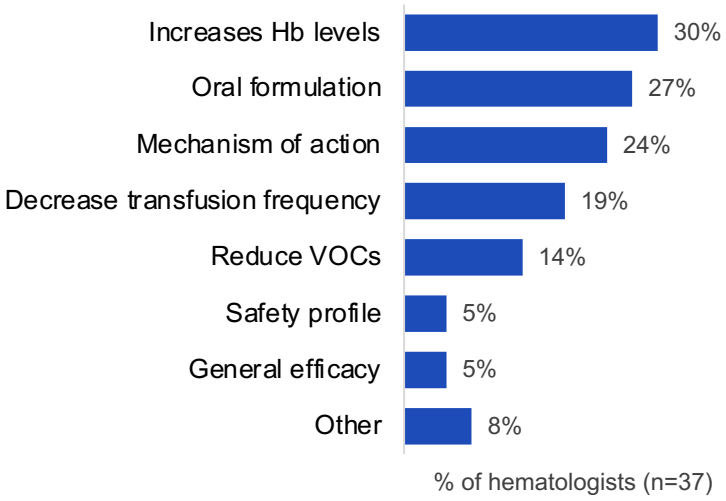
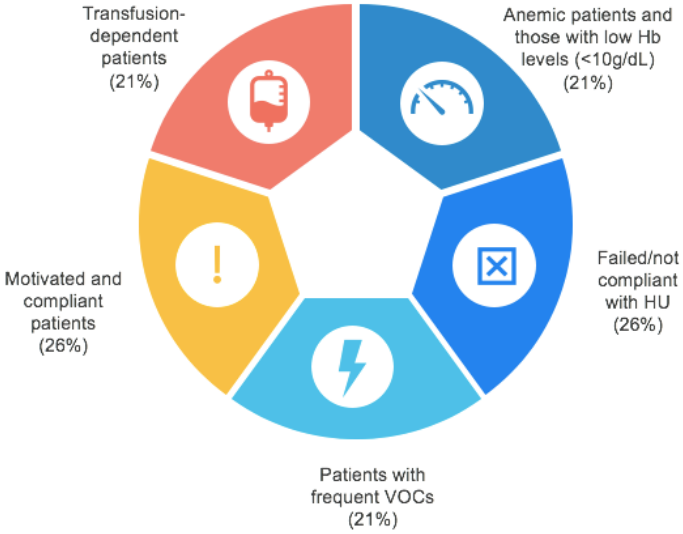


Figure 3.6. Types of patients being treated with Oxbryta[1]



Hematologists' insights on the advantages of Oxbryta (each quote is from a different physician).

"It can improve hemoglobin levels and function and therefore reduce incidence of the complications of sickle cell disease such as pain crises and veno-occlusive events, also seems to reduce transfusion dependence"

"Oral therapy, decreases number of VOCs, transfusion, hospitalizations"

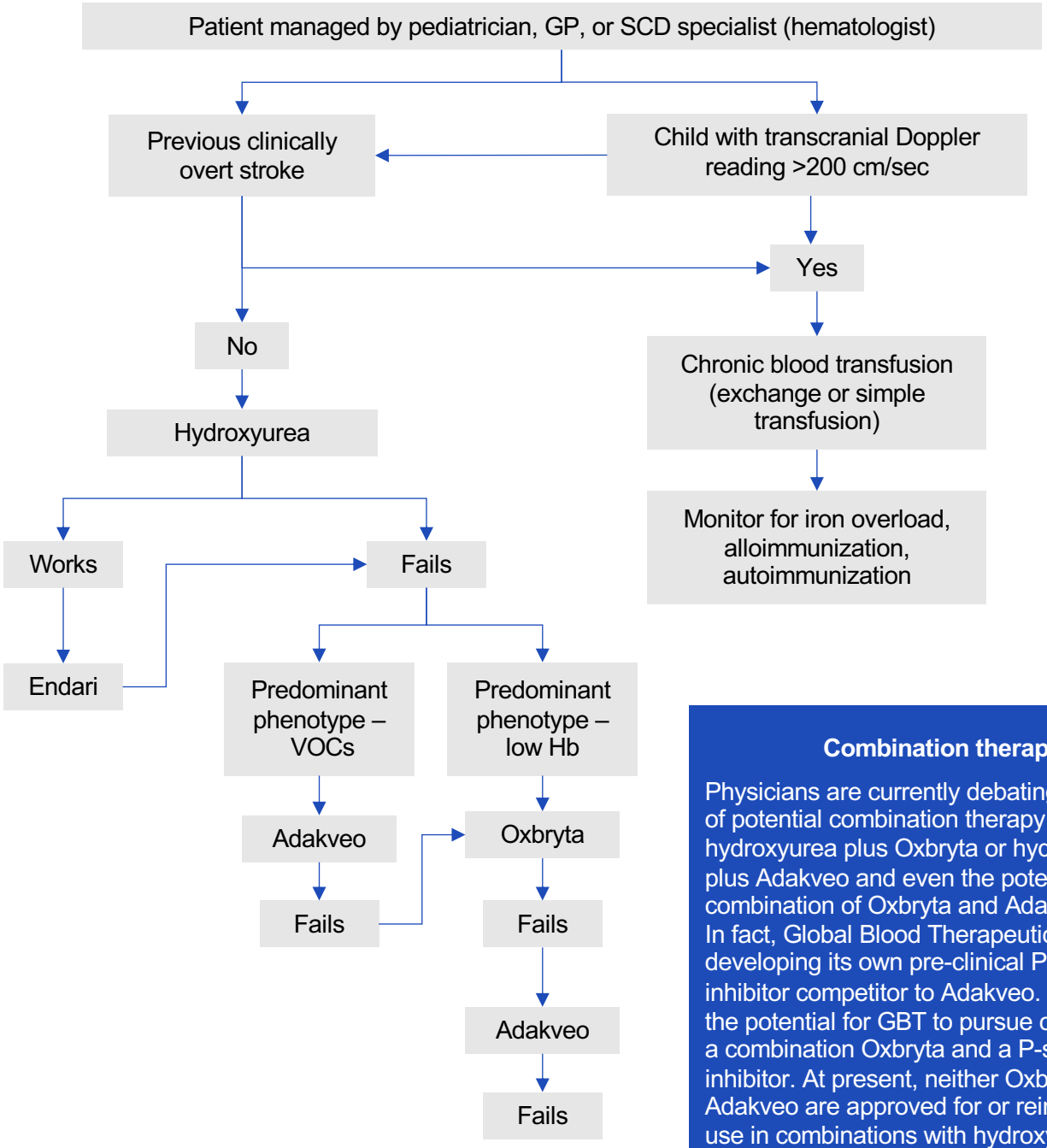
"Orally administered and targets sickling"

"It is ORAL, once daily, that blocks sickle hemoglobin polymerization"

"Well tolerated with minimal side effects"

1. REACH primary market research; see Section 7 on methodology

Figure 3.7. Treatment algorithm for the chronic management of SCD



Combination therapy?

Physicians are currently debating the merits of potential combination therapy of hydroxyurea plus Oxbryta or hydroxyurea plus Adakveo and even the potential combination of Oxbryta and Adakveo therapy. In fact, Global Blood Therapeutics is developing its own pre-clinical P-selectin inhibitor competitor to Adakveo. This sets up the potential for GBT to pursue clinical use of a combination Oxbryta and a P-selectin inhibitor. At present, neither Oxbryta or Adakveo are approved for or reimbursed for use in combinations with hydroxyurea.

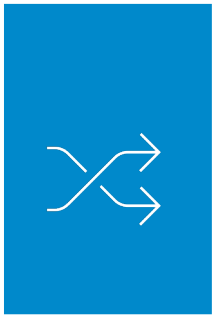
Key treatment dynamics that shape disease management and drug use

There are several nuances in the SCD market that are just as important as the treatments themselves. Most importantly, these market nuances have a significant impact a patient's ability to access care; they include too few adult specialists, a lack of SCD treatment centers, and the absence of a support network when patients transition into adulthood. Regarding treatment, the dawn of combination therapy (which does not exist today) looms large.

Table 3.2. Must-know treatment dynamics for now and the future

There are simply too few adult hematologists that have the skills, expertise, and/or interest in treating SCD patients. Moreover, the absence of comprehensive SCD care centers also leaves patients without resources to help with ongoing management of their condition. As a result, young adult patients lack ongoing care to manage the chronic, progressive nature of the disease throughout adulthood. Instead, they utilize community hospitals that lack SCD specialists and emergency rooms for management of acute pain crises.

Pediatric-to-adult transition is a time when patients can drop out of care and experience treatment lapses and discontinuations. Young adult SCD patients who are no longer under the care of their pediatrician and reaping the benefits of parental oversight to ensure treatment compliance are at a high risk of treatment disruptions. This is particularly impactful in the absence of an adult provider to oversee an integrated care plan.



Future of combination therapy. Today, hydroxyurea is prescribed as a single-agent therapy**.** However, the availability of new therapies with complementary mechanisms of actions to hydroxyurea raise the prospect of combination therapy. Indeed, the transition from monotherapy to combination therapy for SCD has many similarities to the treatment evolution of HIV and Hepatitis C Virus. At present there are no trials evaluating hydroxyurea plus another SCD therapy; however, this is an area worth tracking as it will dramatically alter the treatment paradigm and potentially expand the market for current and emerging therapies.

> *"What we struggle with on the adult side starts and begins with the fact that there are just not enough adult providers. If you look nationally, there are a shortage of sickle cell hematologists. That leads to a big issue with prescribing the standard of care therapy, having the expertise to care for sickle cell, and building a relationship with patients who then, without that expertise, basically bounce around using the ER and the hospital system as their chronic management - which is obviously not effective."*
>
> **- U.S. Adult Hematologist**

The SCD market is poised for increased treatment complexity over the next five to seven years.

Figure 3.8 Timeline of SCD market evolution

"It's possible that we may see patients being treated with Droxia [hydroxyurea] and one of the newer drugs, especially Adakveo so we can try to get the benefits of two separate drugs that do different things to help the patient."

- U.S. Adult Hematologist

"Hydroxyurea, Adakveo, and Oxbryta have essentially kicked the can down the road but we still have the can. They are great additions, but we have so much more need for new treatments."

- U.S. Adult Hematologist

"I feel like we are still early days. Even in the Bluebird trial they went from manufacturing process one to two to three and got a lot better in a short period of time. I think whether it's the stem cell collection or the manufacturing process or the preparative regimen or ancillary therapies – I think there's a lot of room for improvement but it's already looking pretty promising."

- U.S. Adult Hematologist

"There are a number of clinical trials with drugs focused on hemoglobin and VOCs. I think this is great because we shouldn't have to triage which is more significant – the hemoglobin or the pain. So, I think it's a good opportunity to address both. It's like getting the benefits of Adakveo and Oxbryta in a single therapy."

- U.S. Adult Hematologist

"Global Blood therapeutics is developing a new P-selectin inhibitor. I don't think it'll be much better than criz but they would be able to do a trial with their own P-selectin inhibitor and Oxbryta to address VOCs and hemoglobin. If they get approved for that, insurers will have to follow."

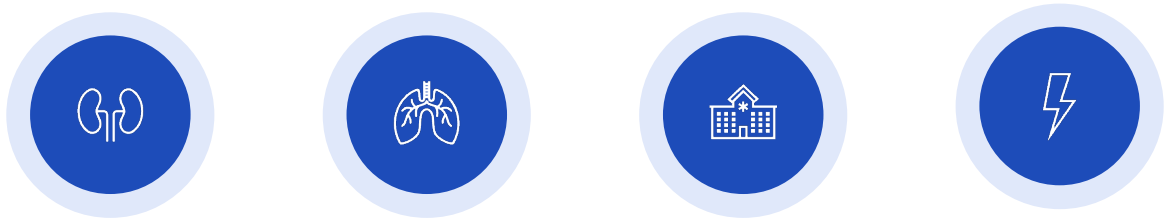
- U.S. Adult Hematologist

4. UNMET NEED

Overview

Surveyed hematologists agree that four areas represent ”extremely” important unmet needs in SCD. The first unmet need is slowing the progression of end organ damage. End organ damage (e.g., stroke, chronic kidney disease, end-stage renal disease, pulmonary hypertension) is a hallmark of SCD disease progression that causes increased morbidity and mortality. Similarly, reducing the incidence of acute chest syndrome, the leading cause of death in SCD patients, is another prominent unmet need that remains despite newly available treatments. Addressing these unmet needs will modify the course of the disease and holds the promise of improving and prolonging life.

Top unmet needs in SCD[1]



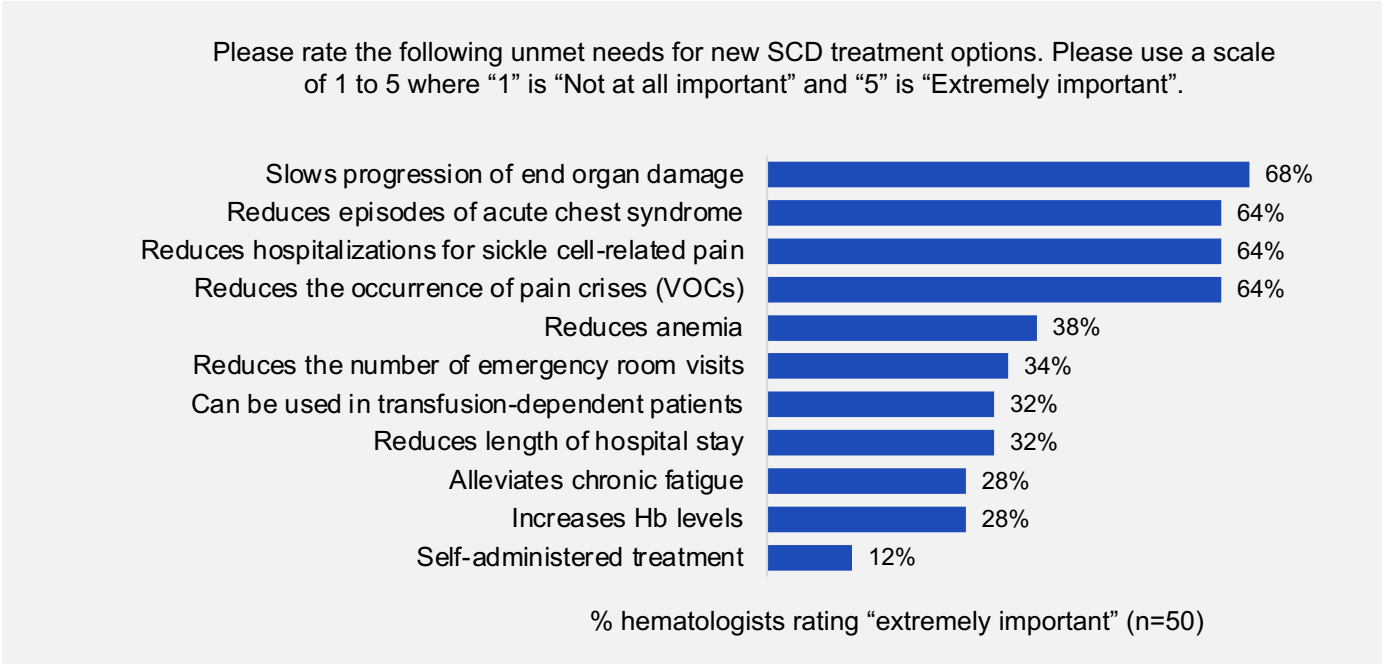
Slow progression of end organ damage

Reduce incidence of ACS especially in children

Reduce hospitalizations for SCD-related pain

Reduce occurrence of VOCs

Figure 4.1. Physician-reported unmet needs in SCD[1]



1. REACH primary market research; see Section 7 on methodology

- Unmet needs highlighted by surveyed and interviewed hematologists are echoed by SCD patients in our ongoing patient research as well as in the FDA's 2014 publication on the "The Voice of the Patient" for SCD.
- SCD patients and caregivers highlight three treatment-related unmet needs:
  - Minimize the long-term progressive end organ damage of the disease
  - Address the underlying causes of sickling and anemia
  - Reduce the daily fatigue and negative cognitive effects of the disease

Table 4.1 FDA Voice of the Patient: insights from different SCD Patients[1]

"We have a lot [of treatments] that are compartmentalized… I would like to see some systematic comprehensive strategies to address the whole person."
"Nothing addresses the tissue damage that's occurring with every single crisis."
"It doesn't matter how much sleep I get or how many vitamins I take, exhaustion is a reality."
"I can deal with the pain, but what… I'm most concerned about is the fact that my organs are dying, my tissues are dying, every time I'm having a sickle cell episode."

Figure 4.2. In the words of SCD patients[1]

Severe, chronic pain limits daily living of SCD patients

- While pain is a prominent feature of the SCD patient experience, its effects extend beyond random episodes and crises that require hospitalization.
- Severe, chronic pain a hallmark of the patient's experience with SCD that affects their daily functioning and ability to spend time with family and friends.
- Patients manage pain with daily pain medications which often dampen or dull the pain but may not eliminate it.

1. The Voice of the Patient. A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative. Sickle Cell Disease. October 2014. https://www.fda.gov/media/89898/download

Figure 4.3. Hematologists' perspective – barriers to patient care[1]

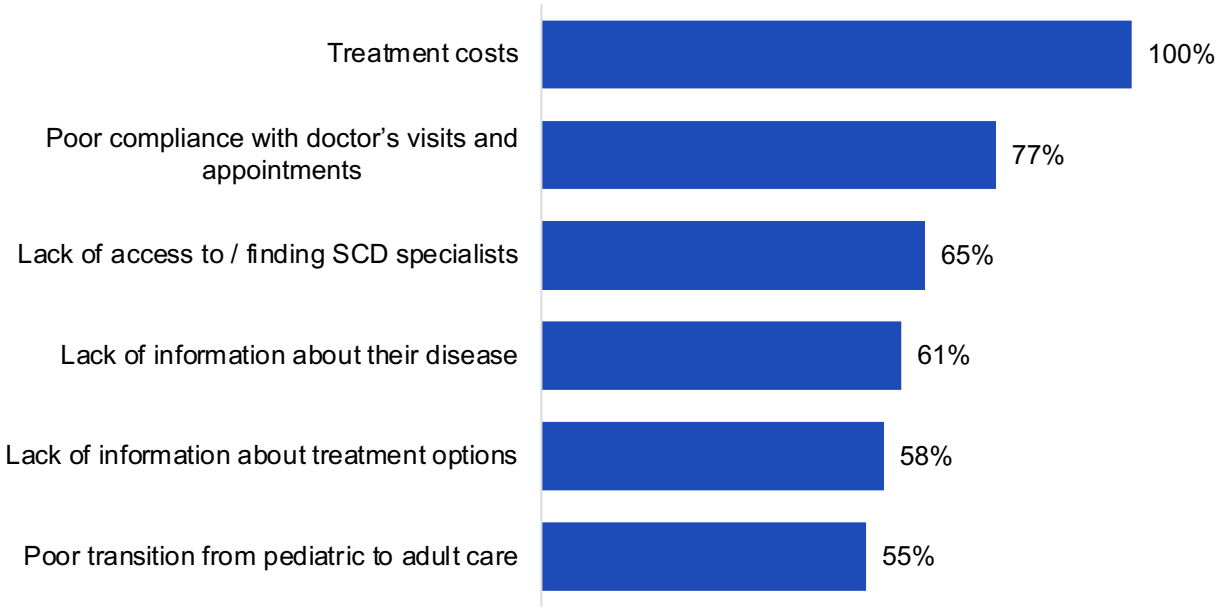
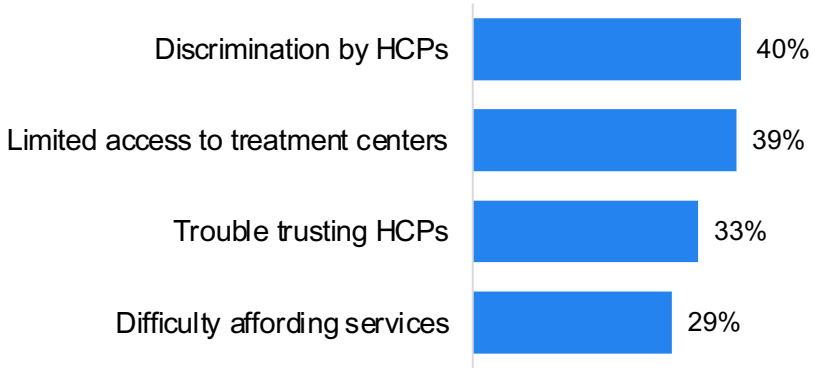


Figure 4.4. The patient's perspective – barriers to care

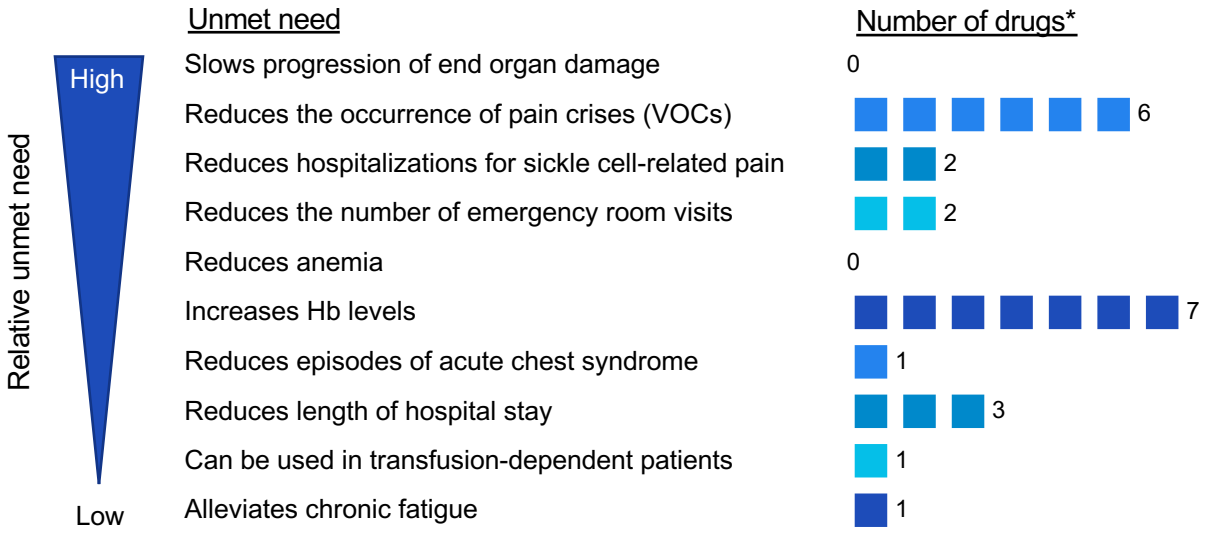


1. REACH primary market research
2. Brennan-Cook J, Bonnabeau E, Aponte R, Augustin C, Tanabe P. Barriers to Care for Persons With Sickle Cell Disease: The Case Manager's Opportunity to Improve Patient Outcomes. Prof Case Manag. 2018 Jul/Aug;23(4):213-219.

5. PIPELINE ANALYSIS

Drug development for SCD is very active, with at least a dozen therapies in clinical development. Most therapies are focused on either reducing the occurrence of VOCs or increasing Hb levels.

Figure 5.1. Number of emerging therapies addressing unmet needs in SCD



* *Some drugs are targeting multiple unmet needs*

Awareness of emerging gene therapy dwarfs awareness of other pipeline agents. When asked if they aware of any treatments or mechanisms of action in development for SCD, only 40% of physicians said "yes". Among this group, a sizeable majority (75%) cited gene therapy. In most instances, hematologists did not differentiate between gene insertion and gene editing.

66% (6 out of 9)
clinical-stage therapies are gene therapies.

40% of hematologists
say they are aware of emerging therapies.

75% of hematologists
with awareness of emerging therapies cite gene therapy.

> *"I'm most excited about gene therapies. I know it's 5-10 years away from now. The proof-of-concept of how to do gene therapy in general is Bluebird Bio. It's a lentiglobin so they're basically doing gene insertion. I'm also interested in how gene editing will go – a couple of companies are there focused on fetal hemoglobin. Early data are pretty remarkable. I think the downstream considerations are costs and strict criteria for who insurers will cover; probably severe patients. There are some long-term effects we'll have to monitor for things like myelodysplasia and the socioeconomic challenges. Patients don't have the support or can't support themselves through this; they often live alone, don't have family or friends that can take time off, and they're far away from centers that can help them do this. So, there's a lot to consider but in the end, right now transplant rates are about 5%; I think transplants including gene therapy will probably increase about 15-20%."*
>
> **- United States, Adult Hematologist**

Summary of clinical-stage emerging SCD therapies

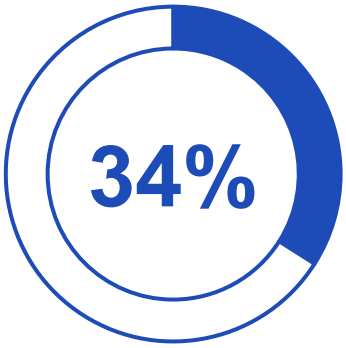
A key hallmark of the pipeline is that most emerging therapies are disease-modifying. Of note, two-thirds of clinical stage emerging therapies are novel, single-treatment gene therapies focused on inserting a functional *HBB* gene (the beta-globin component of hemoglobin) or driving increased expression of HbF in RBCs. Additionally, a handful of once-daily small-molecule therapies are being investigated; these therapies target different mechanisms of action but all aim to improve the health of existing RBCs.

Table 5.1. Emerging SCD therapies, Phase 1 to Phase 3

Company	Molecule	Drug Type	MOA/Target
Phase 3			
Bluebird Bio	BB305	Gene therapy	• Autologous hematopoietic stem cell (HSC) transplantation • BB305 adds functional copies of a modified β-globin gene into a patient's own HSCs allowing their RBCs to produce anti-sickling HbA • **Target Unmet Need:** Reduce VOCs and increase Hb levels
Phase 2			
Novartis	Canakinumab	mAb	• Anti-interleukin antibody targeting inflammation • Marketed under the name Ilaris to treat juvenile arthritis and periodic fever syndromes • **Target Unmet Need:** Reduce daily pain
Aruvant	ARU-1801	Gene therapy	• Autologous CD34+ HSCs and progenitors, transduced with a lentiviral vector encoding a modified γ-globinG16D gene • **Target Unmet Need:** Increase HbF levels
Forma	FT-4202	Small molecule	• Oral therapy that works to help HbS hold on to oxygen more effectively thereby decreasing RBC sickling • **Target Unmet Need:** Reduce VOCs
Phase ½			
Sangamo	BIVV-003	Gene therapy	• Autologous CD34+ HSCs and progenitors designed to induced HbF synthesis • **Target Unmet Need:** HbF levels
Vertex/CRSPR	CTX001	Gene therapy	• Autologous, *ex vivo* CRISPR/Cas9 gene-edited therapy to engineer HbF production • **Target Unmet Need:** Increase Hb levels
Novartis/Intellia	OTQ923	Gene therapy	• CRISPR/Cas9 genome-editing of HSCs to induce HbF production • **Target Unmet Need:** Increase HbF levels
Phase 1			
Bluebird Bio	BCL11a shRNA	Gene therapy	• Autologous CD34+ cells transduced with lentiviral-encoded shRNA that leads to reactivation of the γ-globin • **Target Unmet Need:** Increase HbF levels
Novo Nordisk	EPI01	Small molecule	• Fixed-dose combination of a DNA methyl-transferase enzyme 1 and cytidine deaminase inhibitor (decitabine and tetrahydrouridine) • **Target Unmet Need:** Increase HbF levels • *Ongoing development in question due to absence of new data or company updates since 2018

- The addressable market for gene therapy could be as much as one-third of SCD patients based on hematologists' estimates of the percentage of their patients they think will be gene therapy candidates.
- Physicians are split into two camps when it comes to the types of patients they think are candidates for gene therapy. One group (40%) thinks of gene therapy as a treatment option to prevent the onset of end organ damage. A near equal percentage of clinicians (42%) think gene therapy is most appropriate for those patients with severe disease who have failed current treatments to halt already progressive end organ damage.

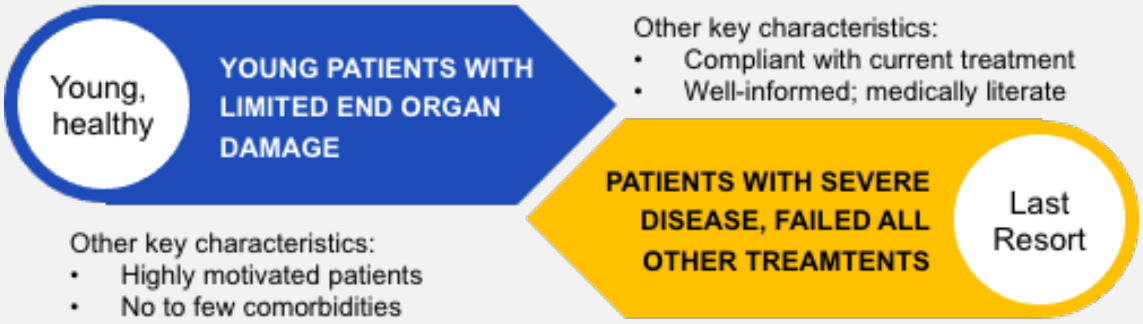
Figure 5.2. Percent of SCD patients who are candidates for gene therapy according to U.S. hematologists[1]



"Gene therapy is potentially a better option than a bone marrow stem cell transplant since patients would not need to rely on finding a perfectly matched donor. I think those that have tried all available treatments, are compliant and still having issues with VOC, acute chest are among the best candidates. But to me with this still being in trial phase, this is a last resort."

– **U.S. Adult Hematologist**

Figure 5.3. Types of patients who are candidates for gene therapy[1]



1. REACH primary market research; see Section 7 on methodology

6. VALUE & ACCESS

Overview. With the annual U.S. list price of Adakveo estimated at $85,000-$113,000 and Oxbryta at $110,000-$125,000, it is no surprise that these drugs have garnered attention regarding their prices (Table 6.1) especially compared to much more affordable therapies (i.e., hydroxyurea, Endari). Hence, it is no surprise that payers have put in place a variety of restrictions on use of Adakveo and Oxbryta (Table 6.2). Beyond high drug prices, SCD patients also struggle with accessing clinicians and treatment centers. In fact, 39% of SCD patients say they have limited access to treatment centers and another 29% of patients say they struggle to afford therapy (Figure. 4.4).

Table 6.1. Current therapy pricing

Drug	List Price (WAC) Per Month
Hydroxyurea	$3
Endari (L-glutamine)	$1,200
Adakveo (crizanlizumab)	$7,000-9,500
Oxbryta (voxelotor)	$10,400

> *"Our patients are on Medicaid and can't afford food. These new drugs are just out of reach for them. Hydroxyurea is a great, cheap drug. We just need to convince people to take it."*
>
> **– U.S. Adult Hematologist**

Table 6.2. Typical commercial payer coverage of Adakveo and Oxbryta

	Adakveo	Oxbryta
Patient age	16 years and older	12 years and older
Prescribing physician	Hematologist	Hematologist
Initial treatment approval		
Hydroxyurea step therapy requirements	Patient currently receiving HU **OR** has a history of treatment failure, intolerance or contraindication to HU	Failure of 6-month trial **OR** at least on VOC in past 6 months while on HU **OR** HU intolerance or contraindication
Other requirements	2 or more VOCs in past 12 months	Hb level ≥5.5 and ≤10.5 g/dL
Concurrent therapy	Cannot be prescribed concurrently with Oxbryta **OR** blood transfusion	Cannot be prescribed concurrently with Adakveo
Approval duration	6 months	6 months
Continued treatment		
Treatment response requirements	Reduced frequency and/or severity of VOCs	Increase in Hb from baseline by 1g/dL
Concurrent therapy	Same as initial approval criteria	Same as initial approval criteria
Approval duration	12 months	12 months

1. Brennan-Cook J, Bonnabeau E, Aponte R, Augustin C, Tanabe P. Barriers to Care for Persons With Sickle Cell Disease: The Case Manager's Opportunity to Improve Patient Outcomes. Prof Case Manag. 2018 Jul/Aug;23(4):213-219.

Key market access dynamics that will continue to shape treatment use

CMS IS THE PREDOMINANT PAYER

The Centers for Medicare and Medicaid Services (CMS) is by far the predominant U.S. payer for SCD: approximately 75% of drug-treated SCD patients are covered by Medicaid or Medicare. Only 1 in 4 patients are covered by private, commercial health insurance. Hence, securing Medicaid approval in key states, particularly the 18 states that account for 85% of diagnosed SCD patients, is critical to the success of any therapy in this market.

HYDROXYUREA STEP THERAPY IS REQUIRED

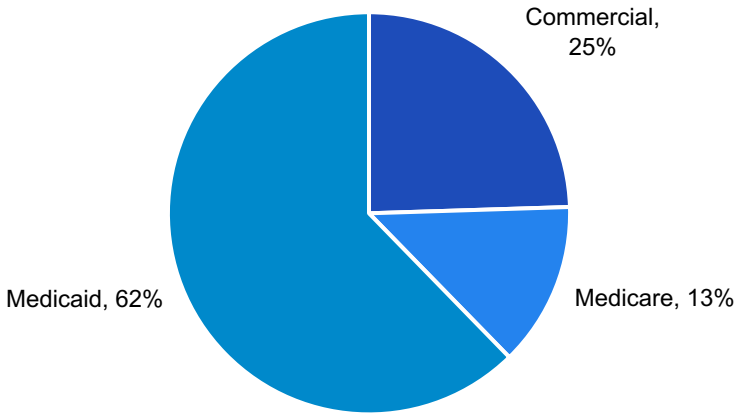
Patient access to new therapies will either require prior failure on, intolerance to, or contraindication for hydroxyurea (Figure 6.2). Given that only 55% of SCD patients take hydroxyurea (Figure 3.1), it is likely that hydroxyurea step therapy will be an effective limitation on use of much pricier Adakveo and Oxbryta.

PATIENT SERVICES AND SUPPORT ARE PARAMOUNT FOR SUCCESS

Given the demographics of the SCD patient population, new brands will need to be prepared for a significant investment in patient support that includes:

- Care Coordinators
- Nurse Support Team
- Financial assistance programs for commercially-insured patients
- Referrals to independent charitable patient assistance programs for help with items such as copayments, health insurance premiums, and travel costs.

Figure 6.1. SCD patients by insurance type[1]



1. Centers for Medicare & Medicaid Services, 2020. At a Glance: Medicaid and CHIP Beneficiaries with Sickle Cell Disease (SCD), T-MSIS Analytic Files (TAF) 2017. https://www.medicaid.gov/medicaid/quality-of-care/downloads/sickle-cell-disease-infographic.pdf

7. METHODOLOGY

Primary Market Research Approach

Participants : U.S. Hematologists (paid an honorarium for participating)

Dates: July 1 to July 10, 2020

Quantitative survey: 15-minute online survey (n=50 respondents)

Qualitative interviews: 1-hour phone interview (n=4 respondents)

Participant Screening Criteria

Respondents had to meet the following requirements to participate in this study

- **Time Spent in Clinical Practice:** More than 75% of devoted to direct patient care as opposed to non-clinical activities such as research or teaching
- **Time in Practice**: Minimum of 2 years and no more than 30 years
- **Patient Load:** Minimum of 5 sickle cell disease patients seen in a typical month

Interviewed Physicians

Physician	Hospital	Unit
Nirmish Shah, MD	Duke University Hospital	Adult Comprehensive Sickle Cell Center
Michael Callaghan, MD	Children's Hospital of Michigan	Sickle Cell Center
Laura DeCastro, MD	Pittsburgh University	Research Center of Excellence, Sickle Cell Disease
Susan Claster, MD	University of California Irvine Medical Center	The Center of Comprehensive Care Inherited Blood Disorders

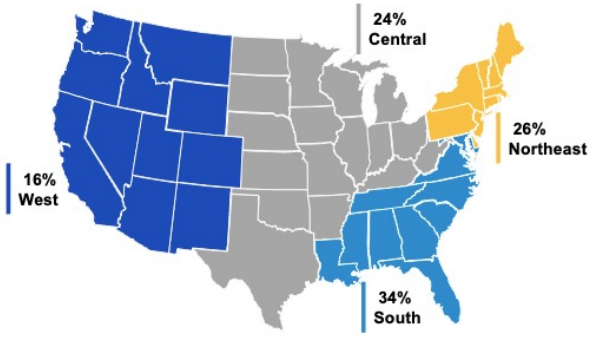
Hematologist Practice Overview

75%+
Time spent in clinical practice

14
Years in practice (average)

46%
Practicing in an academic hospital
- 38% in office practice
- 16% in community hospital

Practice Location



24%
Pediatric hematologists

76%
Adult hematologists

56%
Practicing in a SCD treatment center

Average of 216 patients seen in SCD treatment centers

Disease Definition.

In this study, we define cases of SCD as individuals with one of the following genotypes.

- Hemoglobin Sβ0 thalassemia
- Hemoglobin Sβ+ thalassemia
- Hemoglobin SC
- Hemoglobin SD
- Hemoglobin SE
- Hemoglobin SS

Prevalence Estimates.

We systematically reviewed the published literature, including online registries and surveys, using a systematic search with a defined date range, for the most representative epidemiological data on SCD. We identified two studies that satisfy our quality criteria for inclusion.

- Brousseau DC, Panepinto JA, Nimmer M, Hoffmann RG. The number of people with sickle-cell disease in the United States: national and state estimates. Am J Hematol. 2010 Jan;85(1):77-8.
- Hassell KL. Population estimates of sickle cell disease in the U.S. Am J Prev Med. 2010 Apr;38(4 Suppl):S512-21.