health action council

New Treatment Options for Sickle Cell Disease

Casgevy® and Lyfgenia® Approved as First Gene Therapies for Sickle Cell Disease

On December 8, 2023, the U.S. Food and Drug Administration (FDA) approved Vertex/CRISPR Therapeutics' Casgevy® (exagamglogene autotemcel) and bluebird bio's Lyfgenia® (lovotibeglogene autotemcel), for the treatment of patients 12 years of age and older with Sickle Cell Disease (SCD). Casgevy® and Lyfgenia® are the first cell-based gene therapies approved for SCD, and Casgevy® represents an innovative advancement in the field of gene therapy as the first FDA-approved treatment to utilize a type of novel genome editing technology.

Background

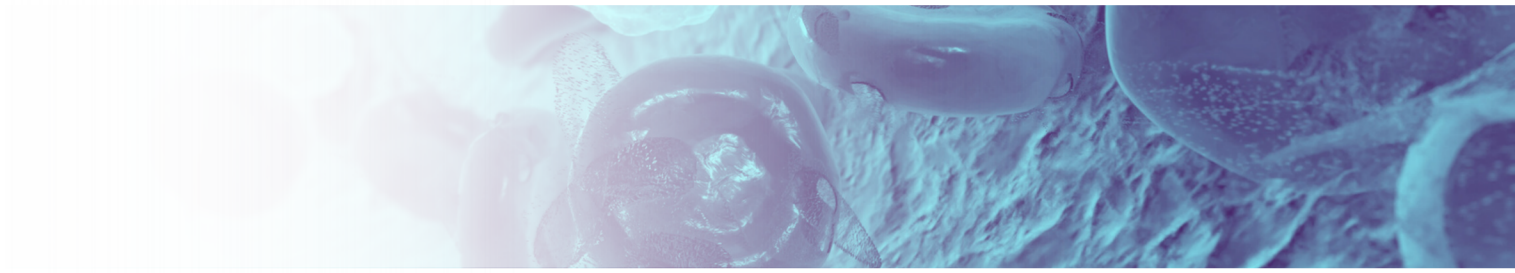
SCD is a group of genetically inherited red blood cell disorders that affect hemoglobin, the protein that carries oxygen through the body. Normally, red blood cells are disc-shaped and flexible enough to move easily through the blood vessels. In sickle cell disease, red blood cells become crescent- or "sickle"-shaped due to a genetic mutation. These sickled red blood cells do not bend or move easily and can block blood flow to the rest of the body. The blocked blood flow through the body can lead to serious problems, including stroke, eye problems, infections, and episodes of pain called 'pain crises'.

The condition affects more than 100,000 people in the United States and 20 million people worldwide. In the United States, most people who have sickle cell disease are of African ancestry or identify themselves as Black.

- About 1 in 13 Black or African American babies are born with sickle cell trait.
- About 1 in every 365 Black or African American babies are born with sickle cell disease.

Many people who come from Hispanic, Southern European, Middle Eastern, or Asian Indian backgrounds also have sickle cell disease.

Patients with SCD often experience severe pain related to vaso-occlusive crises (VOCs) and other complications, resulting in significantly higher hospitalization rates and emergency department utilization rates compared with the general population.



SCD Treatments

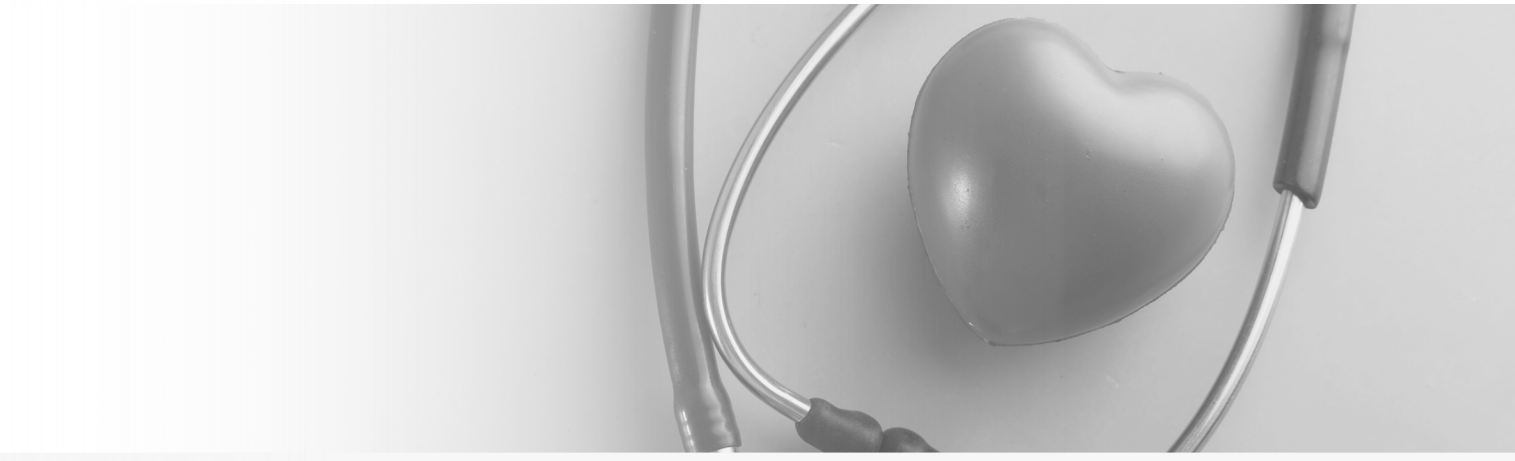
For some children and teenagers, a stem cell (bone marrow) transplant might cure the disease. Stem cell transplant is recommended only for people, usually children, who have significant symptoms and complications of sickle cell anemia. Blood transfusions are also a treatment option used to treat and prevent complications, such as stroke, but they are not curative.

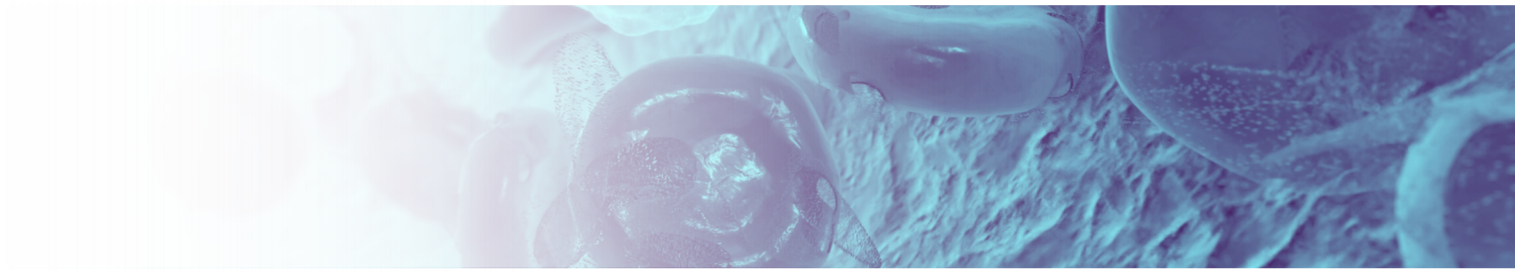
For most patients, the traditional approach to treatment is symptomatic management, to relieve pain and help prevent complications of the disease. One medication, Voxelotor may be used to prevent sickling of red blood cells, which lowers the risk for anemia and improves blood flow to organs. In order to reduce pain crises that are common with SCD, multiple options exist:

- Hydroxyurea (oral) has been shown to reduce or prevent several complications of SCD and has been a mainstay of therapy as a first-line agent. It helps to reduce frequency of pain crises and lower the need for transfusions and hospital stays.
- ·L-glutamine (oral) helps to reduce frequency of pain crises.
- Adakveo injections can help to reduce frequency of pain crises.
- Other traditional pain remedies, including opioids

The approval of Casgevy® and Lyfgenia® represent a new treatment option, one that is potentially curative. Casgevy® is approved for the treatment of SCD in patients 12 years of age and older with recurrent VOCs. Lyfgenia® is approved for the treatment of patients 12 years of age and older with SCD and a history of VOC events.

Both treatments are administered as one-time infusions and are made from a patient's own blood stem cells, which are modified and returned to the patient. Both therapies require the patient to undergo myeloablative conditioning (destruction of native stem cells) prior to infusion of the modified cells. Patients who receive Casgevy or Lyfgenia will be followed in a long-term study to evaluate each product's safety and effectiveness.





Benefits of Casgevy® and Lyfgenia®

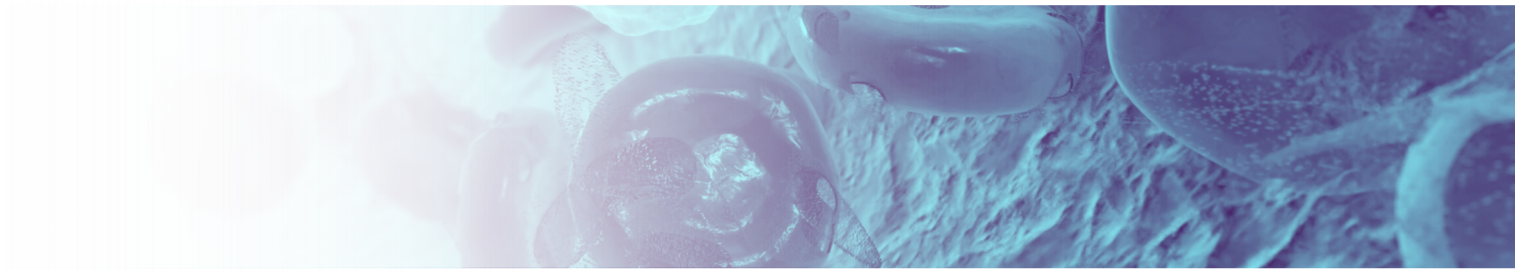
Casgevy is the first FDA-approved gene therapy that uses CRISPR/Cas9-editing technology for genetic modification. In the ongoing single-arm, multicenter CLIMB-121 trial in adult and adolescent patients 12 to 35 years of age with SCD, a total of 44 patients were treated with Casgevy. Of the 31 patients with sufficient follow-up time to be evaluable, 29 (93.5%) achieved the primary efficacy outcome, freedom from severe VOC episodes for at least 12 consecutive months during the 24-month follow-up period. In addition, all treated patients achieved successful engraftment with no patients experiencing graft failure or graft rejection.
Approval of Lyfgenia, which uses a lentiviral vector for genetic modification, is based on the analysis of data from the single-arm, 24-month multicenter HGB-206 study in patients with SCD and a history of vaso-occlusive episodes (VOEs) who were between 12 and 50 years of age. Effectiveness was evaluated based on complete resolution of VOEs (VOE-CR) between 6 and 18 months after infusion with Lyfgenia. In the trial, 28 (88%) of 32 patients achieved VOE-CR during this time period.

[With Casgevy, an edit (or "cut") is made in a particular gene to reactivate the production of fetal hemoglobin, which dilutes the faulty red blood cells caused by sickle cell disease. Lyfgenia, on the other hand, uses a viral envelope to deliver a healthy hemoglobin-producing gene.]

Although both of these agents show tremendous promise, it will take years to know the long-term effects and durability of the treatment. Based on the clinical trial results to date, not all patients who receive the treatments will respond favorably. Current and future clinical trials may help elucidate inter-patient response rates.

Pricing Perspective for Casgevy® and Lyfgenia®

As with all types of gene therapies approved to date, both treatments will come at an extreme cost: Vertex and CRISPR set pricing for Casgevy at $2.2 million, and bluebird bio has priced Lyfgenia at $3.1 million. These costs do not include the cost of all of the care associated with treatment, like chemotherapy or hospital stays.
The Institute for Clinical and Economic Review (ICER), a nonprofit organization that assesses drug costs, concluded that despite uncertainty regarding longer-term outcomes, Casgevy and Lyfgenia are both estimated to produce substantial gains in length and quality of life. ICER evaluated both Casgevy and Lyfgenia, comparing the treatments with each other and with the standard of care, which included hydroxyurea, blood transfusions, and other supportive care. ICER released an updated final evidence report in August 2023, indicating that gene therapies for SCD would be cost-effective if priced between $1.35 million and $2.05 million per treatment.



Key Considerations for Payers

The approval of Casgevy and Lyfgenia are significant for a number of reasons:

- Until now, the only possible cure for sickle cell disease was a bone marrow transplant, which has its own set of costs and challenges.
- Casgevy and Lyfgenia may be a one-treatment cure for many patients.
- Compared to the ultra-rare conditions in which other gene therapies are used, SCD is much more prevalent in the U.S. population and can have more significant budget impacts on payers.

Uptake of these new therapies is expected to be slow, due to safety concerns, unknown long-term benefit, prescriber resistance to treatment, and high cost

Patients likely to be eligible for therapy generally include those who:

- Have an eligible genotype
- Age is in line with labeled indication (currently 12 years and older)
- Have “severe” SCD, based on number and severity of VOEs/VOCs
- Have “severe” SCD, based on number and severity of VOEs/VOCs, while being treated appropriately with Hydroxyurea
- Do not have access to sibling-matched stem cell transplant donor (as this offers possibility of cure)
- Otherwise match clinical trial criteria

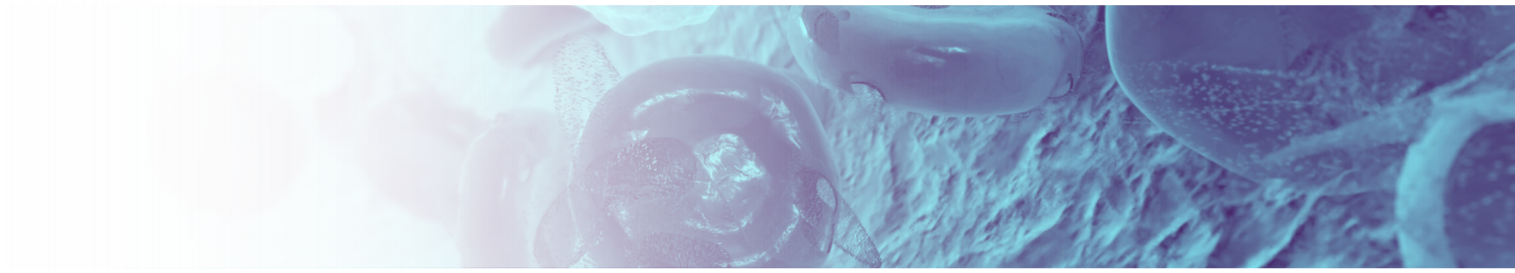
Casgevy therapy will likely be limited to patients with a documented SCD genotype and a history of at least two severe VOC events per year (four in 24 months), similar to the clinical trial inclusion criteria, and whose disease is not sufficiently managed with transfusion or existing drug therapies.

Lyfgenia will likely only attract patients with the most severe, uncontrolled SCD symptoms, similar to those eligible for allogenic hematopoietic stem cell transplant (HSCT).

Safety continues to be a major concern with these products, particularly due to the myeloablative conditioning required prior to treatment with both products.

Hematologic malignancy has occurred in patients treated with Lyfgenia. The label includes a Boxed Warning with information regarding this risk. Patients receiving Lyfgenia should have lifelong monitoring for these malignancies.

Most recent clinical trials for genetic therapies have limited the duration of follow-up. Demonstrated long-term durability of cure will be key in establishing the therapies’ clinical value and justifying their price, which may limit initial uptake until more patients have been followed for longer periods of time.



Key Considerations for Payers *(Continued)*

Many of the approximately 16,000 - 20,000 people that are estimated are eligible for Casgevy or Lyfgenia in the U.S. are covered by Medicaid.

Carriers and PBMs are currently working on value/outcomes-based contracts for Casgevy and Lyfgenia, details of which have not yet been shared.

Similar to other gene therapies, coverage of these treatments will be limited to the medical benefit.

For self-funded employers with stop-loss insurance, the stop-loss carriers will be evaluating the impact of this new therapies. Generally, stop-loss policies would not reimburse for Casgevy and Lyfgenia if not covered in the underlying plan document. However, coverage in the underlying plan document does not necessarily mean the stop-loss policy would cover and reimburse. Even if plan mirroring is in place, there could be policy limitations and exclusions that would not align with the underlying plan document.

Whether or not the Embarc Benefit Protection Program (through Evernorth/Cigna), CVS/Aetna's Financial Protection Program, or UHC/OptumRx's Gene Therapy Risk Protection program will include Casgevy and Lyfgenia is not yet known, as it is still being evaluated.

Vertex will make Casgevy available at nine sites across six states and Washington, D.C., while Bluebird said that 27 centers in 12 states are now ready to receive patient referrals for Lyfgenia.

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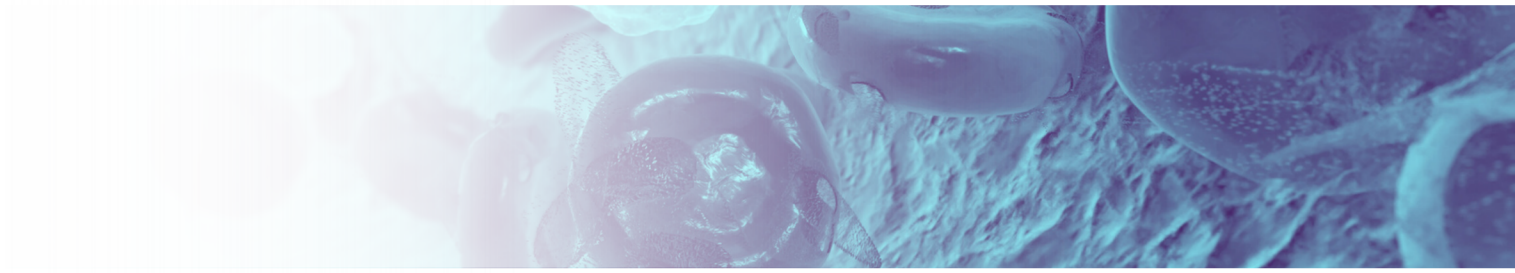

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Health Action Council is a not-for-profit 501(c)(6) organization representing mid and large-size employers that works to improve human and economic health through thought leadership, innovative services, and collaboration.

It provides value to its members by facilitating projects that improve the quality and moderate the cost of healthcare purchased by its members for their employees, dependents, and retirees.

Health Action Council also collaborates with key stakeholders health plans, physicians, hospitals and the pharmaceutical industry to improve the quality and efficiency of healthcare in the community.

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