# Emerging Gene Therapies for Sickle Cell Disease

**Revised Background and Scope**

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## Background

Sickle cell disease (SCD) is an inherited blood disorder caused by a genetic mutation of the *HBB* gene responsible for the β-globin component of hemoglobin; hemoglobin is the protein in red blood cells that carries oxygen. To have clinically significant disease, an individual typically must have two affected copies of the *HBB* allele: either two copies of the specific sickle mutation (HbSS) or one copy with the sickle mutation compounded with another abnormal variant of the *HBB* gene (e.g., sickle-beta thalassemia). The resulting abnormal hemoglobin makes red blood cells prone to take on an abnormal sickle shape, particularly when oxygen levels are low in the cell, and also reduces their ability to carry oxygen, which in turn can make sickling worse. This shape is also more rigid and "sticky," two features that drive the pathophysiology of SCD: vascular obstruction and ischemia; and a shortened lifespan and early destruction (hemolysis) of red blood cells.[1] Individuals with only one copy of HbS do not typically experience these sequelae and are considered to be carriers or have "sickle cell trait."

The clinical manifestations of obstruction, ischemia, and hemolysis can be severe. Recurrent acute pain crises, or vaso-occlusive crises (VOC), are one of the most prevalent manifestations of SCD and the largest driver of morbidity and mortality. Patients can also experience other serious health complications such as acute chest syndrome (a life-threatening pulmonary complication), serious infections, stroke, renal necrosis, and priapism.[2] Chronic complications can emerge across multiple organs and include delayed puberty, avascular necrosis, skin ulcers, chronic pain, neurocognitive impairment, chronic kidney injury, pulmonary hypertension, cardiovascular disease, and can result in early mortality.[2] Resultant health care costs are high, with the total health system economic burden of SCD estimated at $2.98 billion per year in the United States (US) with 57% due to inpatient costs, 38% due to outpatient costs, and 5% due to out-of-pocket costs.[3] The incidence of SCD is estimated at 300,000 to 400,000 live births globally per year. In the US, the current best prevalence estimate is approximately 100,000 individuals with SCD, although comprehensive surveillance and reporting is lacking and the exact number of cases in the US is unknown.[4]

The impact of SCD on quality of life is complex and affects both patients and their caregivers in many ways. In addition to the health-related impact of disease, many other factors further diminish

quality of life. The lack of treatment options, discrimination, stigma around the need for acute and chronic pain management, disruption of family and social activities, missed school and/or work all combine to make living with SCD very difficult.[5] We heard from both patients and clinicians that the picture of "baseline" or "usual" care for patients with SCD is highly variable. Deep dysfunction in care is driven by poor coordination within provider systems and by barriers to access that arise from a broad range of factors including systemic racism, uninformed clinicians, poverty, and insurance systems poorly designed to coordinate coverage for patients with multi-system chronic conditions.

The severity of SCD, even in those with HbSS disease, is variable from patient to patient. One modifier of severity is the amount of other forms of hemoglobin produced, including fetal hemoglobin (HbF), which does not include a β-globin component. While production of HbF typically nearly disappears by age one, patients with SCD can have substantial continued production of HbF, perhaps due to the stress from hemolysis.

Hydroxyurea is considered the mainstay of treatment for SCD and has been shown to be effective at reducing the number of acute VOCs, reducing complications, and improving quality of life. The mechanism of action of hydroxyurea is not fully understood, but it is believed to work by increasing the HbF content of red blood cells and also by altering the adhesion and rigidity of sickled cells and by reducing neutrophil activation. Some individuals may require chronic transfusions to treat anemia and prevent serious complications of SCD (e.g., stroke) and pain management is often required for supportive care. Newer therapies are available, but they are generally reserved for cases of treatment failure with hydroxyurea (i.e., l-glutamine [Emmaus], crizanlizumab [Novartis]) or for patients who are on hydroxyurea but have persistent hemolytic anemia (i.e., voxelotor [Global Blood Therapeutics]). We heard from experts that uptake in clinical practice is still quite low, and the Institute for Clinical and Economic (ICER) previously found that the prices of these newer therapies are not aligned with their clinical benefits.[6]

Hematopoietic stem cell therapy (HSCT) is considered the only curative treatment for SCD. Ideally HSCT is performed with a human leukocyte antigen (HLA)-matched sibling donor. When performed at a younger age (<14 years of age) and with a sibling match, the five-year event-free-survival is likely 95% or higher for transplants performed in recent years. However, graft-versus-host disease is still a serious risk, many patients do not have a compatible related or unrelated donor, and the risks of HSCT increase with age.[9]

Lovotibeglogene autotemcel ("lovo-cel," bluebird bio) and exagamglogene autotemcel ("exa-cel," Vertex Pharmaceuticals and CRISPR Therapeutics) are emerging potentially curative gene therapies for SCD. Lovo-cel works by using a modified virus (lentivirus vector) to insert a functioning version of the *HBB* gene into the patient's own stem cells. This is accomplished by retrieving stem cells from the patient's blood, engineering them outside of the body, and then transplanting the cells with functioning *HBB* back into the body. The patient must receive chemotherapy to prepare the bone marrow to receive the corrected cells and to produce new red cells with normal β-

globin/hemoglobin, but the regimen of chemotherapy is generally less intense than in HSCT. A closely related product for beta thalassemia was recently reviewed in another ICER report. Exa-cel employs similar procedures (e.g., autologous transplantation of modified cells), but rather than relying on a viral vector to insert a functioning gene, it utilizes a gene editing approach using CRISPR-based technology to turn off the age-related suppression of HbF and thus increase the amount of HbF in red blood cells. The manufacturers for both lovo-cel and exa-cel are expected to submit their Biologics License Application to the Food and Drug Administration in early 2023.

## Stakeholder Input

This scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of gene therapies.

During our prior review, we heard extensively from patients and patient groups about the significant impact of SCD. Many patients had difficulty working or staying in school. Many lost jobs or dropped out of school because of frequent or prolonged absences due to acute SCD-related events. Family members described some of the impacts of caregiving, including the need to leave the work force to provide care. Both individuals and families reported significant financial hardship as a result of SCD. In addition to lost wages, patients and their families reported significant out-of-pocket costs due to the disease.

Some patients and family members described making decisions to avoid marriage to maintain health insurance or forego having children to avoid passing on the gene to the next generation. Families often had multiple members affected by SCD and described the emotional pain from watching parents, children, and siblings suffer and then die at an early age. A number of patients reported serious problems with mental health issues such as depression, anxiety, and suicidal thoughts.

We heard repeated concerns that there are not enough doctors and other medical providers adequately trained in the management of SCD. This resulted in patients either not having good access to local medical care or inconsistent care across various health care settings. We also heard that patients had often been perceived as drug-seeking, resulting in important delays in getting adequate pain medication, and for some even life-saving interventions. This was further heightened by racism and bias against the populations of color most affected by SCD. Patients and family members were frustrated by the lack of good information or medical education on their disease. They expressed additional frustration caused by the lack of available therapies for their condition relative to other diseases. They were also concerned that even when new treatments

become available, there will be delays in access due to lack of provider knowledge. While there is enthusiasm for new therapies, patients also want to know that those therapies are safe and effective in the long term.

## Report Aim

This project will evaluate the health and economic outcomes of lovo-cel and exa-cel for SCD. The ICER Value Framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

## Applicable Framework Adaptations

We propose to assess lovo-cel and exa-cel under an adaptation of the ICER Value Framework for treatments of high-impact "single and short-term therapies (SST)" because we believe they meet the following criteria defined as:

- The therapy is delivered through a single intervention or a short-term course (less than one year) of treatment that offers a significant potential for substantial and sustained health benefits extending throughout patients' lifetimes. The therapy can eradicate a disease or condition or produce sustained major health gains that can halt the progression of significant illnesses.

## Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality single-arm trials and systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction,

and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

## Populations

The population of focus for this review is adolescents and adults with severe SCD who do not have a matched sibling donor or haploidentical donor for HSCT or are too old for safe HSCT. There is no generally accepted classification of SCD severity; in the studies of the agents under review, patients were required to have a minimum of four severe vaso-occlusive events in the prior two years.

Data permitting, we intend to assess evidence on treatment for SCD for groups stratified by:

- Age
- Genotype (e.g., HbSS, SC, SD)

## Interventions

The full list of interventions is as follows:

- Lovotibeglogene autotemcel (lovo-cel) (bluebird bio)
- Exagamglogene autotemcel (exa-cel) (Vertex and CRISPR Therapeutics)

## Comparators

Data permitting, we intend to compare both agents to standard of care (may include hydroxyurea and chronic blood transfusions) and to each other.

## Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Acute pain crisis (i.e., vaso-occlusive crisis)
    - Chronic pain
    - Hospitalization
    - Mortality
    - Fatigue
    - Cognitive effects
    - Acute chest syndrome
    - Mental health effects (e.g., depression, anxiety)
    - Cardiovascular events (e.g., stroke and silent infarcts, pulmonary hypertension, heart failure)

    - Hearing loss
    - Vision loss
    - Organ damage
    - Infertility and pregnancy complications
    - Sexual dysfunction
    - Quality of life
    - Ability to work or attend school
    - Other adverse events including:
        - Serious adverse events (e.g., delayed neutrophil engraftment, thrombocytopenia, malignancies)
        - Adverse events related to gene therapy treatment
- Other Outcomes
    - Laboratory evidence of SCD severity
        - Hemoglobin (e.g., total Hb, HbF, HbAT87Q, HbS)
        - Hemolysis markers (e.g., reticulocyte count, indirect bilirubin levels, haptoglobin, lactate dehydrogenase)
    - Caregiver impact
    - Health resource utilization

## Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration that meet the study design criteria set forth above and measure the outcomes of interest.

## Settings

All relevant settings will be considered, including inpatient, outpatient/clinic, office, and home settings.

## Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

**Table 1. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages**

| Contextual Consideration* |
|---|
| Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability |
| Magnitude of the lifetime impact on individual patients of the condition being treated |
| Other (as relevant) |

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

| Potential Other Benefit or Disadvantage* |
|---|
| Patients' ability to achieve major life goals related to education, work, or family life |
| Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life |
| Patients' ability to manage and sustain treatment given the complexity of regimen |
| Society's goal of reducing health inequities |
| Other (as relevant) |

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

## Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost effectiveness of the treatments of interest relative to relevant comparator treatments. The model structure will be based in part on a review of prior published models of SCD. The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per quality-adjusted life year (QALY), and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. As in the clinical evidence review, the comparative value analyses will follow the SST Value Framework adaptations including the addition of the conservative and optimistic scenarios as well as the shared savings analyses.

The target population will consist of adolescent and adult patients with severe SCD, defined as having a minimum of four severe vaso-occlusive events in two years and clinically eligible to

undergo bone marrow conditioning and who do not have an HSCT matched donor. A cohort of patients will transition between states during annual cycles over a lifetime time horizon (using a 3% discount rate for costs and outcomes), modeling patients from treatment initiation until death. In addition, cost effectiveness will be estimated for shorter time horizons (e.g., five years).

Key model inputs will include clinical probabilities, quality-of-life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using clinical trial results for each treatment. As data permit, relevant subgroup analyses (e.g., by age, severity, chronic transfusion) will be explored.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events, and direct medical costs. The health outcome of each intervention will be evaluated in terms of VOCs avoided, life years gained, QALYs gained, and equal value of life years gained (evLY). Quality-of-life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLY gained, cost per life year gained, and cost per VOC avoided.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact may be found here.

## Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by lovo-cel and exa-cel (e.g., reductions in VOCs), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of SCD beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

# References


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