Gene Therapies for Sickle Cell Disease

Final Evidence Report

August 21, 2023

Prepared for

July 8, 2025: New evidence regarding treatments and therapies gets published on an ongoing basis. ICER reached out to key stakeholders included in this review more than 12 months after the publication of this report giving them an opportunity to submit public comments regarding new relevant evidence or information on coverage that they wish to highlight. Their statements can be found here. ICER has launched ICER Analytics to provide stakeholders an opportunity to work directly with ICER models and examine how changes in parameters would affect results. You can learn more about ICER Analytics here.

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None of the above authors disclosed any conflicts of interest defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care manufacturers or insurers.

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Francesca Beaudoin served as the lead author for the report. Dmitriy Nikitin led the systematic review and authorship of the comparative clinical effectiveness section in collaboration with Avery McKenna. Praveen Thokala developed the cost-effectiveness model and authored the corresponding sections of the report. Jon Campbell, Eldon Spackman, David M. Rind, and Steven D. Pearson provided methodologic guidance on the clinical and economic evaluations. The modeling team would like to thank Marina Richardson and Ashton Moradi for sharing their expertise and resources, which were valuable in developing the cost-effectiveness model. We would also like to thank Laura Cianciolo, Kelsey Gosselin, Emily Nhan, and Becca Piltch for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 24% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/pharmacy benefit managers and life science companies. There are no life science companies relevant to this review who participate in this program. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

About CTAF

The California Technology Assessment Forum (CTAF) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CTAF seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The CTAF Panel is an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about CTAF is available at https://icer.org/who-we-are/people/independent-appraisal-committees/ctaf.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/wp-content/uploads/2022/11/Sickle-Cell-Disease-Key-Stakeholders-List_112322.pdf

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Table of Contents

List of Acronyms and Abbreviations Used in this Report

ASCT	Autologous stem cell transplant
evLY	Equal value life year
FDA	Food and Drug Administration
g/dL	gram per deciliter
GVHD	Graft-versus-host disease
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem cell transplantation
ICER	Institute for Clinical and Economic Review
QALY	Quality-adjusted life year
SCD	Sickle cell disease
US	United States
VOC	Vaso-occlusive crisis
VOE	Vaso-occlusive event

Executive Summary

Sickle cell disease (SCD) is a broad term referring to a group of inherited blood disorders caused by mutations in *HBB,* the gene that encodes the beta (β) subunit of hemoglobin. The rigid and inflexible sickle shape of erythrocytes (red blood cells) results in hemolysis and vaso-occlusion with numerous profound downstream consequences on the health and wellbeing of affected people. The incidence of SCD is estimated at 300,000 to 400,000 live births globally per year. In the United States (US), it is estimated that approximately 100,000 people are living with SCD, although the exact prevalence is unknown.[2]

Recurrent acute pain crises, or vaso-occlusive crises (VOC), are a hallmark manifestation of SCD. Patients can also experience serious acute medical complications such as acute chest syndrome, life-threatening infections, acute splenic sequestration crisis, stroke, and priapism.[3] Chronic complications affecting nearly all organ systems often develop as patients age, including delayed puberty, avascular necrosis, skin ulcers, chronic pain due to recurrent bone infarctions, neurocognitive impairment, chronic kidney disease, pulmonary hypertension, cardiovascular disease, and can result in early mortality.[3] Associated health care costs are high, with the total economic costs of SCD estimated at $2.98 billion per year in the US.[4] This does not even consider other economic costs (e.g., childcare, missed work) nor impacts on quality of life. Quality of life of both patients and their caregivers is adversely affected by not only the health-related burden of disease, but also by limited treatment options, discrimination, stigma, inadequate pain management, disruption of family and social activities, and missed school and/or work.[5]

In the most severe forms of SCD, standard of care usually involves hydroxyurea, as-needed blood transfusions, and supportive care for acute pain crises and other acute and chronic complications. Hematopoietic stem cell transplantation (HSCT) is currently the only potentially curative treatment for SCD, but HSCT has a risk of graft failure/rejection, graft-versus-host disease (GVHD), acute complications during the transplant process, and carries at least 4% risk of mortality even with a perfectly matched sibling donor that carries less risk of GVHD and graft failure. There is a lack of compatible donors (especially donors that are related to the patient) and thus most people with SCD are not able to pursue HSCT as a therapeutic option even if there is interest.

Lovotibeglogene autotemcel ("lovo-cel," bluebird bio) and exagamglogene autotemcel ("exa-cel," Vertex Pharmaceuticals and CRISPR Therapeutics) are emerging transformative 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 whereas exa-cel utilizes a gene editing approach using CRISPR-based technology to increase the amount of fetal hemoglobin in red blood cells by deleting a portion of the *BC11A* gene. The manufacturers for both lovo-cel and exa-cel have had their Biologics License Application (BLA) to the Food and Drug Administration (FDA) accepted in June 2023; regulatory decisions on both therapies are expected in December of 2023.

We compared the therapies with each other and with standard of care consisting of supportive care, hydroxyurea, and blood transfusions in some patients. In trials of both therapies, the main outcome was the number of vaso-occlusive events or crises (VOEs or VOCs) over two years of follow-up. In the pivotal lovo-cel trial, 90% of participants achieved complete resolution of all VOEs between six and 18 months after lovo-cel infusion and 30 of 31 patients were free of *severe* VOEs. In a single trial of exa-cel in 35 participants, only 17 participants had 12 months of follow-up for the primary study outcome available for review, of which 16 (94.1%) were free of severe VOCs during that time. In both trials of both lovo-cel and exa-cel, serious adverse events were observed in the trials. Although serious adverse events were attributed to myeloablative conditioning, they were not infrequent and chemotherapy is required before receiving both lovo-cel and exa-cel. However, uncertainty still remains about the long-term degree of risk of gene therapies in the real world. At one point, FDA placed a clinical hold on lovo-cel due to safety concerns surrounding hematologic malignancies; there have been two cases of acute myeloid leukemia that resulted in death. The events were felt not to be due to the gene insertion but were atypical events for SCD patients and will be important to follow closely over the long term as more patients receive these gene therapy treatments. It is also not known whether results from the trial will generalize to a broader population of people with SCD who might not have met trial eligibility criteria.

In considering net health benefit, the marked improvement seen with lovo-cel in a small number of patients with severe SCD needs to be balanced with the potentially severe harms of myeloablative conditioning in SCD and uncertainties about duration of benefit. For people with severe SCD, we conclude that lovo-cel provides at least an incremental net benefit compared with standard of care and may provide a substantial net health benefit. We rate this comparison as "Incremental or Better" (B+).

Exa-cel presents similar concerns with additional uncertainties given the small number of patients treated to date and that CRISPR therapy is even newer than lentiviral gene therapy. For people with severe SCD, we conclude that compared with standard of care, treatment with exa-cel may be comparable, result in incremental net benefit, or result in substantial net benefit. We rate this comparison as "Comparable or Better" (C++).

Comparing lovo-cel with exa-cel, we rate the evidence as "Insufficient" (I). Given the different mechanisms of action, it is possible that future research may identify differences in effectiveness or safety between the two therapies.

We modeled each therapy compared with standard of care over a lifetime time horizon. We assumed identical efficacy for the two therapies given the small number of people studied. The Health Benefit Price Benchmark (HBPB) for treatment with either lovo-cel or exa-cel ranges from $1,350,000 to $2,050,000.

Although uncertainties about durability and harm remain, both lovo-cel and exa-cel are likely to substantially improve quality and length of life among patients with SCD. Ultimately, cost effectiveness will depend on the actual prices for these therapies.

Appraisal committee votes on questions of comparative effectiveness and value, along with key policy recommendations regarding pricing, access, and future research are included in the main report. Several key themes are highlighted below:

- All stakeholders have a responsibility to ensure equitable and optimal patient access to gene therapies for sickle cell disease (SCD) (i.e., lovo-cel and exa-cel).
- Even though potentially curative gene therapies should and will command a high price, manufacturers should align prices with independent estimates of the patient-centered therapeutic value of their treatments; in the context of significant uncertainty regarding longer-term safety and durability of benefits, prices should be set at the lower end of a reasonable cost-effectiveness range.
- Coverage for gene therapy should be provided in a comprehensive fashion, including coverage for travel, ancillary care pre- and post-procedure (including mental health care), fertility preservation, and out-of-pocket financial burden.
- Manufacturers should work with payers to create meaningful alternative payment models that can address two key distinguishing features of gene therapies: 1) the significant short-term budget impact; and 2) the considerable uncertainty regarding longer-term safety and benefits.

ICER is not issuing an access and affordability alert for gene therapies for SCD. Although pricing is not yet known for either lovo-cel or exa-cel, we heard from multiple stakeholders that initial uptake of these therapies is unlikely to be rapid. As such, we do not expect that the number of patients treated within five years will result in costs exceeding the ICER potential budget impact threshold of $777 million per year.

1. Background

ICER reviewed non-curative therapies for sickle cell disease (SCD) in 2021; much of the background information in this report is updated from that review. 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, a person 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.[6] People with only one copy of the sickle mutation (HbS)and who do not co-inherit other hemoglobin abnormalities do not typically experience these sequelae and are considered to be carriers or have "sickle cell trait."

The clinical manifestations of microvascular obstruction, ischemia, endothelial damage, and hemolysis can be severe. Acute pain crises, or vaso-occlusive crises (VOCs), are one of the most prevalent manifestations of SCD and the largest driver of morbidity. A substantial proportion of patients experience recurrent, severe, VOCs, averaging several events each year that can lead to hospitalization.[7] 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.[3] Chronic complications can emerge across multiple organs and include delayed puberty, avascular necrosis, skin ulcers, chronic pain, neurocognitive impairment, chronic kidney injury, pulmonary hypertension, and cardiovascular disease, and SCD can result in early mortality.[3] Resultant health care costs are high, with the total health system economic burden of SCD estimated at $2.98 billion per year in the United States (US) with 57% due to inpatient costs, 38% due to outpatient costs, and 5% due to out-of-pocket costs.[4] 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 people with SCD, although comprehensive surveillance and reporting is lacking and the exact number of cases in the US is unknown.[2]

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 increase the difficulty of living with SCD.[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, which does not include a β-globin component. While production of fetal hemoglobin typically nearly disappears by age one for people without hemoglobin disorders, most SCD patients have some residual fetal hemoglobin expression. The amount of residual fetal hemoglobin is highly variable from patient to patient and higher levels of fetal hemoglobin expression typically result in fewer short- and long-term complications of SCD.

Hydroxyurea is considered the mainstay of treatment for SCD and has been shown to be effective at reducing the number of acute VOCs, reducing chronic complications, and improving quality of life and survival. The exact mechanisms of action of hydroxyurea are not fully understood, but the primary benefits are derived by increasing the fetal hemoglobin content of red blood cells, by altering the adhesion and rigidity of sickled cells, and by reducing neutrophil production. Some people with SCD, particularly those with a history of stroke or other serious complications, may require chronic (lifelong), monthly blood transfusions to prevent additional complications. Regular transfusions create additional challenges including the need for long-term chelation therapy (e.g., deferoxamine) to avoid serious health complications (e.g., heart and liver disease) of resultant iron overload.[8] Many people with SCD require multidisciplinary care and acute and chronic pain management as supportive care for complications related to their SCD. While highly effective, chronic transfusion therapy carries its own risk and expense including iron overload, allo-immunization, problems with vascular access, and rare infectious complications. Newer therapies are available, but they are generally reserved for people with persistent or frequent painful episodes despite hydroxyurea therapy (i.e., l-glutamine [Emmaus], crizanlizumab [Novartis]) or persistent, severe hemolytic anemia (i.e., voxelotor [Global Blood Therapeutics]). We heard from experts that although these therapies may also be an alternative for people with SCD who do not want to take hydroxyurea, their uptake in clinical practice is still quite low and we previously found that the prices of these newer therapies are not aligned with their clinical benefits.[9,10]

Hematopoietic stem cell transplantation (HSCT) is currently the only potentially 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.[11,12] However, graft-versus-host disease (GVHD) is still a serious risk, many patients do not have a compatible sibling-matched donor (preferred option), and the risks of HSCT increase with age.[13]

Lovotibeglogene autotemcel ("lovo-cel," bluebird bio) and exagamglogene autotemcel ("exa-cel," Vertex Pharmaceuticals and CRISPR Therapeutics) are transformative gene therapies with the

potential for clinical cure of 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 myeloablative chemotherapy to prepare the bone marrow to receive the corrected cells and to produce new red cells with normal β-globin/hemoglobin. 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 one of the genes known to suppress fetal hemoglobin and thus increase the amount of fetal hemoglobin in red blood cells. The Food and Drug Administration (FDA) accepted bluebird bio's Biologics License Application (BLA) of lovo-cel for priority review on June 21, 2023, and the revised Prescription Drug User Fee Act (PDUFA) date is set for December 20, 2023. Similarly, the FDA accepted Vertex Pharmaceuticals' and CRISPR Therapeutics' BLA for exa-cel for priority review on June 9, 2023, and the revised PDUFA date is set for December 8, 2023.

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route
Lovotibeglogene autotemcel (lovo-cel)	Lentiviral addition of anti-sickling Hb, HbAT87Q	IV infusion following myeloablative conditioning chemotherapy
Exagamglogene autotemcel (exa-cel)	CRISPR/Cas9 gene-edited cell therapy targeting BCL11A to increase fetal Hb	IV infusion following myeloablative conditioning chemotherapy

Hb: hemoglobin, IV: intravenous

2. Patient and Caregiver Perspectives

This report was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review and incorporates feedback gathered during calls with stakeholders. We have included patient and caregiver perspectives from ICER's 2021 report on non-curative therapies for SCD, updated with new insights from additional stakeholder input. 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 preventive treatments.

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

An All-Encompassing Condition

Patients, family members, clinicians, and other members of the sickle cell community conveyed that for someone without SCD, it is hard to understand the physical, emotional, and mental toll of SCD. Pain crises are an enormous burden to the patient not only when they are happening, but due to their accumulated negative impact over the years. It is a danger to minimize the impact of the condition by characterizing it as pain crises alone because of the cumulative multitude of adverse effects that impact both physical and mental health.[14] The range of acute adverse effects of SCD include painful crises, but also life-threatening events such as strokes and blood clots. These acute effects also contribute to long-term risks for additional major organ dysfunction such as congestive heart failure and liver failure.[15] Other health effects such as chronic pain also play an enormous role in daily living. In addition to both acute and chronic effects on almost every major organ system, there is an enormous impact on quality of day-to-day life.

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

People living with SCD and others emphasized that there is truly an all-encompassing biopsychosocial impact of disease that is hard to capture, particularly in the setting of research. People with SCD not only described intense fatigue, anxiety, and depression, but at times extreme hopelessness. One person told us that pursuing a curative option allowed them to

"give up on giving up." The condition presents challenges at home, school, work, and social relationships.[16] People with SCD often end up on formal disability programs, which unfortunately carry stigma.

This is not to say that people with SCD are unable to function at a high level in society, but that the challenges and the barriers faced are distinct from other chronic health conditions. One of the most important perspectives we learned from the SCD community was that SCD remains a misunderstood and marginalized condition. To fully appreciate the potential benefits of new treatments, a broad appreciation for the impact of SCD on the lives of patients and their families must be achieved and must be kept front and center when making judgments about the value of these treatments.

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

Stigma and Limitations on Daily Life

People living with SCD may appear healthy. An outward appearance of wellbeing can present additional barriers to appropriate care and contribute to social stigmas surrounding the disease. A general lack of awareness about the disease among nurses, hospitalists, and society at large means that healthy-looking people with SCD suffering from an acute pain crisis, acute chest syndrome, or other SCD-related complication may not be taken seriously. Patients presenting at the emergency room may be made to wait longer before receiving attention.[17,18] One particularly concerning anecdote that was recorded in the FDA's *Voice of the Patient* report described a child who was sent back to class by the school nurse after suffering a central nervous system event because he was "deemed unruly."[5] We also heard patient testimony of young men being called "perverts" because they were experiencing priapism. Misperceptions about appearance, coupled with a lack of SCD awareness in broader communities, can lead to bias both in and out of the health care setting. People living with SCD who are unable to participate in their daily commitments at work or school due to insurmountable fatigue, pain, or other complications may be accused of laziness or subject to bullying. Children and their caregivers felt SCD challenged their ability to perform well in school and work.[16] Chronic daily pain, fatigue, and the sudden onset of acute pain crises increase absenteeism make it difficult to concentrate, disrupt school and social interactions, and create a lot

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

of stress and anxiety. SCD can cause neurocognitive impairment; some people with the disease have reported difficulty remembering tasks, retaining what they learn in school, and difficulty staying engaged and focused on school activities.[19-21] Some children reported frustration and social isolation from limitations on their ability to participate in physical activities, travel on long flights, play outside in cold weather, or swim in unheated water. One person with SCD who had undergone curative therapy told us that they now enjoy winter sports and swimming, something unimaginable before treatment. Although SCD is an inherited condition, a lack of societal awareness about the disease leads some people to hide their diagnoses so their peers will not misperceive them as contagious.

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

Family members described the tremendous responsibility of caregiving, including the need to leave the work force to provide care for their loved ones while facing the impact of lost wages and significant out-of-pocket expenses. Adults with SCD reported difficulty in maintaining employment because of frequent, unexpected, or prolonged absences due to acute SCD-related events. Some people with SCD and their 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. We heard from a number of stakeholders that mental health issues such as depression, anxiety, and suicidal thoughts are common; such statements are corroborated in the clinical literature.[14,16,22]

Racial Bias

We heard consistently from people with SCD, family members, clinicians, and other members of the sickle cell community that the experience of living with SCD and all aspects of its treatment are mired in racism. Although SCD affects people of different races and ethnicities, it has historically been viewed in the US as a "Black disease."[1,23] Racism and implicit bias presents substantial obstacles to care in what is already a condition with high morbidity and mortality.[1]

We heard frustration from the sickle cell community about the lack of investment in research or comprehensive treatment centers that might increase access to better treatment, improve health outcomes, and reduce other disparities faced by SCD patients and their families. Historically, SCD

has been underfunded with no breakthroughs or developments in two decades. Although the populations of people living with other severe hereditary conditions such as cystic fibrosis are significantly smaller than that of SCD, these conditions often receive greater funding for research and treatment. Cystic fibrosis, for example, affects approximately 30,000 people in the US (vs. about 100,000 with SCD) and receives seven to 11 times the amount of funding per patient.[17,24,25] Structural racism as well as implicit bias affect the allocation of resources toward research, health care delivery, and quality improvement.[26,27]

Pain Relief

Racial bias and treatment disparities for people with SCD have been well documented, particularly when it comes to pain management. Patients who present at emergency departments may experience delays in treatment and diagnosis as well as inadequately treated pain.[1,17,28-31] We heard from some people that they dress in professional attire while in crisis before going to the emergency department in an effort to avoid categorization as drug-seeking. People with SCD expressed a hesitancy to reveal any familiarity with pain regimens they know to be effective out of fear they would be denied relief and labeled as drug-seeking. We heard that many adults with SCD have an advocate accompany them on visits to an emergency department to increase their chance of receiving appropriate treatment for pain.

Health inequity in the management of pain is compounded by racial bias and stigma of the condition itself, including beliefs about opioid use and addiction. A survey of more than 100 physicians who care for people with SCD suggested that provider attitudes toward substance use disorders can have negative implications for patients, including undertreatment of pain and discrediting a patient's report of pain severity.[17,29] Furthermore, a 2014 study of attitudes toward patients with SCD among 215 emergency department providers (nurses and physicians) found that relative to physicians who have less frequent and shorter interactions with patients, nurses had greater levels of negative attitudes toward patients with SCD; nurses expressed more frustration in caring for patients, estimated a higher prevalence of opioid use disorders among patients, and reported less unease with the ways in which their colleagues treated patients.[17,30]

The ongoing opioid epidemic has further complicated a person's ability to access pain medicine, as doctors have grown increasingly wary of prescribing opioids. Many state laws, payer coverage policies, and hospital protocols follow "one size fits all" approaches to pain management, which limit dosing or cease dispensing after a predetermined period of time, irrespective of whether a person's pain is adequately managed. The recently revised Clinical Practice Guideline for Prescribing Opioids for Pain (2022) from the Centers for Disease Control specifically excludes SCD, acknowledging the important role of opioids in pain management and the dangers of inadequate pain management. In addition, the Centers for Medicare and Medicaid Services recently issued a policy to recommend that Medicare beneficiaries with SCD be exempt from opioid safety

restrictions; similar exemptions have been recommended in some state Medicaid programs, although such policies will not improve patient access if provider attitudes do not also change.[17,32,33]

Lack of Specialists and Optimal Treatment

People with SCD lamented that education and awareness among clinicians (even among hematologists) is severely lacking and that this exacerbates problems accessing high quality care. Patients commonly receive care from generalists, emergency nurses, and hospitalists who may be less equipped to help them manage their disease.[17,34,35] We heard repeated concerns that there were not enough doctors and other medical providers who are adequately trained in the management of SCD, particularly for adults. A national survey of over 3,000 family physicians

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

revealed that only 20% of respondents felt comfortable treating SCD.[34,35]

Clinical experts and people with SCD alike commented that incompetent care can be catastrophic; we heard several anecdotes about deaths that might have been prevented had the person received care from a more knowledgeable provider. People with SCD are conscious of the deaths and irreversible damage that result from long wait times in the emergency room as well as the increased mortality from events that occur in the hospital; they reported feeling intense anxiety and stress about going to the hospital, sometimes delaying, or avoiding seeking necessary care. We also heard that some people experience post-traumatic stress disorder following severe episodes of illness.

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

"Too often sickle cell patients are marginalized, treated with stereotypical idealism and inherent bias that ultimately leads to them avoiding going for help or simply not receiving it in their greatest time of need, during the VOC. This leads to many damaging side effects including death but more so the damage taking place in their bodies while they are lingering in an untreated state of ongoing necrosis taking place throughout their bodies!" – Person living with SCD

While the management of pediatric patients with SCD has improved dramatically in recent years, the transition from pediatric to adult care coincides with a period of high risk for many people as SCD often worsens during the late teens/early twenties. There is a significant shortage of adult care providers with the requisite knowledge and skill set. People with SCD described the difficulty they faced trying to navigate a very different system of care and recounted a worsening of health as a result of limited access to multidimensional care. Because of the course of SCD, there is a sharp increase in mortality following the transition from pediatric to adult care.[36,37]

"Finding a great doctor that knows information about sickle cell is like finding a needle in a haystack." – Person living with SCD

This problem is magnified in smaller cities, towns, and rural areas where people report needing to travel several hours to see a specialist, participate in a clinical trial, or access treatment through compassionate use programs. People with SCD were anxious that the retirement of a community's only specialist would lead to a spike in SCD mortality. A retired specialist from California, Dr. Keith Quirolo, provided sobering statistics about the severe shortage of sickle cell hematologists: in the state of California, there are only about five physicians who specialize in the treatment of SCD for every 7,000 residents living with the condition.[34] In response to these health disparities, legislative efforts the Sickle Cell Disease Comprehensive Care Act have been made to establish federal funding for state Medicaid programs to create special centers to provide comprehensive, preventive outpatient care. Policy such as this would be a step toward equitable access to life-saving standard of care.

Attitude Toward Gene Therapies

There is consensus in the SCD community about the dire need for disease-modifying drugs and curative therapies. Over the past several years, few treatment options aside from analgesia were available. Enthusiasm for gene therapy stems from not only interest in a cure, but also concerns about current treatments' effectiveness, accessibility, and side effects (e.g., running to the bathroom from gastrointestinal side effects of L-glutamine, hair loss from hydroxyurea). Stakeholders identified the importance of community engagement in the research and development of new therapies, but key challenges were noted including inherent trust issues between members of the SCD community and the clinical/research community, challenges

identifying members of the SCD community to participate in engagement, inconsistency with definitions of SCD variants between the research community and SCD community, and lack of longitudinal data collection regarding people and disease progression.

> *"The quality of life for most sickle cell patients is a life of extreme suffering from pain and rejection of medical care. We are stigmatized as drug seekers because there are hardly any tools a care provider can offer us but pain killers. Life is painful and frustrating, and we have few choices in our options for care." – Person living with SCD*

There is cautious optimism about gene therapies that may soon become available. One person with SCD described her feelings as both "joy and apprehension" – joy at the prospect of a cure and apprehension related to a new therapy with unknown long-term effects. We spoke with people who had received curative treatment (either HSCT or gene therapy as part of a trial) and they all cited life-changing improvements in their health and quality of life. While they acknowledged that there was risk and uncertainty with curative therapies, they felt that their health had deteriorated to a point that potential benefit far outweighed potential risks.

People living with SCD and their families worry about being able to afford the treatment itself and other costs associated with treatment such as fertility preservation. It is possible also that there are other financial costs that are unknown at this time. People with SCD expressed concern that high drug prices may cause insurance policies to implement barriers to access. Access to high quality, standard of care is already difficult for many people living with SCD. People are concerned that doctors will not know enough about the new therapies and that many people with this condition do not live in areas where they will have ready access to emerging gene therapies. Both patients and clinicians expected gene therapies to be available only at major medical centers or centers of excellence. People also wonder whether they will be eligible for treatment with these new treatments. We heard from some people with SCD that they fear they will be too old or have too much organ damage to be candidates for gene therapy.

Finally, stakeholders emphasized the importance of multidisciplinary care. New therapies need to be integrated into treatment plans that care for the whole patient. Care coordination across different systems and payers was underscored as a huge area of unmet need.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review assessing the evidence on lovo-cel and exa-cel for the treatment of severe SCD are described in Supplement Section D1. A research protocol is published on Open Science Framework and registered with PROSPERO (CRD42023385515).

Scope of Review

We reviewed the clinical effectiveness of lovo-cel and exa-cel versus standard of care for the treatment of severe SCD. We also intended to compare lovo-cel to exa-cel via any evidence directly comparing the two therapies or by indirect comparisons of key outcomes. We sought evidence on patient-important outcomes, including resolution of VOCs, health-related quality of life, and adverse events. The full scope of the review is described in Supplement Section D1.

Evidence Base

lovo-cel

Our evaluation of lovo-cel consists of two trials, HGB-205 and HGB-206. Upon completion of these trials (~two years), participants were eligible to enroll in a long-term follow-up study, LTF-307.

HGB-205 was a Phase I/II proof of concept trial that evaluated lovo-cel infusion in three patients with severe SCD. HGB-206 is the pivotal Phase I/II trial of lovo-cel for the treatment of severe SCD. Changes to the treatment protocol and enrollment criteria resulted in three study cohorts: Group A, B, and C (see Supplement Table A1). Patients in the Group C cohort underwent a revised method of stem cell collection to enhance the transduction process (plerixafor mobilization and apheresis vs. bone marrow harvesting), thereby improving gene insertion such that later cohorts received a greater cell dose than earlier cohorts, including patients in the HGB-205 trial. bluebird bio is seeking approval for lovo-cel in the US on the basis of clinical data from Group C and as such, efficacy and safety data from this cohort will be the primary focus of this review.

Trial participants of HGB-206 were aged 12 to 50 with severe SCD (βS/βS, βS/β0, or βS/β+ genotype) (Table 3.1). Group C required a minimum of four severe VOEs in the 24 months prior to enrollment; this was a more stringent eligibility criterion that was implemented after several participants had already been enrolled. Therefore, not all Group C members had a baseline of four or more severe VOEs. Trial participants were also required to have had an intolerance to hydroxyurea or occurrence of VOEs despite hydroxyurea treatment as well as an ability to carry out normal activities of daily living with some assistance. Participants were ineligible for the trial if they had a

willing, matched HLA-identical sibling hematopoietic cell donor. A history of overt stroke was later added to the study exclusion criteria; five participants had received infusion of lovo-cel prior to the protocol amendment.

A total of 36 Group C patients received lovo-cel infusion; participants had a median age of 24 years and experienced a median of three severe VOEs per year in the two years prior to trial enrollment.[38,39] Additional trial enrolment criteria and baseline characteristics are outlined in Supplement Tables D4 and D5.

HGB-210 is an ongoing single-arm multi-site Phase III trial of lovo-cel in patients ages two to 50 with severe SCD with an estimated study completion date of September 2025 (see Supplement Table D13). The number of participants in the trial and the duration of the follow-up period was not adequate to be incorporated into the evidence base.

LTF-307 is a long-term follow-up study that will evaluate the safety and efficacy of lovo-cel in participants continuing from trials HGB-205, 206, and 210 for an additional 13 years.

Table 3.1. Overview of Pivotal lovo-cel Clinical Study

Trial	Study Design	Population	Key Baseline Characteristics
HGB-206	Phase I/II, single-arm, open-label, nonrandomized trial Follow-up: 24 months	People aged 12 to 50 with severe SCD (βS/βS, βS/β0, or βS/β+ genotype) and ≥4 severe VOEs in the 24 months prior to informed consent Group A N=7 Group B N=2 Group C N=36	Group C Cohort: Median age (range): 24 (12-38) Female sex: 37% βS/βS genotype: 100% Annualized rate of severe VOEs in last 24 months, median (range): 3.0 (0.5-13.5) Total Hb, median: 8.5 g/dL

dL: deciliter, g: gram, Hb: hemoglobin, N: total number, SCD: sickle cell disease, VOE: vaso-occlusive event

exa-cel

The pivotal trial of exa-cel is CLIMB-121, an ongoing single-arm Phase I/II/III trial of 35 participants. Persons ages 12-35 with severe SCD and a history of greater than two severe VOCs per year in the two years before screening were enrolled.[40] Patients who had an available HLA-matched related donor, prior HSCT, or clinically significant active infection were excluded from this study. The estimated study completion date is October 2024; efficacy and safety data from a pre-specified interim analysis are reported using a data cut-off of September 2022. Additional trial information can be found in Supplement Tables D4 and D6.

Patients who have completed the two-year follow-up period of CLIMB-121 are eligible for a long-term follow-up study, CLIMB-131.

Table 3.2. Overview of Pivotal exa-cel Clinical Study

Trial	Study Design	Population	Key Baseline Characteristics
CLIMB-121	Phase I/II/III, single-arm, open-label, nonrandomized trial Follow-up: 24 months post-transplant	People aged 12 to 35 with severe SCD and a history of ≥2 severe VOCs per year in 2 years before screening N=35	Mean age (range): 22.1 (12-34) Female sex: 45.7% βS/βS genotype: 94.3% βS/β0 genotype: 5.7% Annualized rate of severe VOC in last 24 months, mean (range): 4.2 (2-18.5) Total Hb, mean: 9.1 g/dL*

dL: deciliter, g: gram, Hb: hemoglobin, N: total number, SCD: sickle cell disease, VOC: vaso-occlusive crisis
*Data are from an earlier cut-off date of February 2022 (N=30)

3.2. Results

Clinical Benefits

Primary Outcomes

The primary outcome for both interventions was the proportion of trial participants who were free of VOE/VOCs post-treatment (Table 3.3). Both study outcomes included the occurrence of acute chest syndrome, splenic sequestration, and priapism in their definition of an acute pain episode. A visit to a medical facility was a component in both severe outcomes.

While there are similarities in the outcome definitions between lovo-cel and exa-cel, a few differences are noted. The definition of a severe VOC in the exa-cel trial was more broadly inclusive as compared to the severe VOE in the lovo-cel trial, which included a time component as a measure of severity. A non-severe occurrence of a VOC was not measured in the exa-cel CLIMB-121 trial. While the lovo-cel protocol did not include reference to the administration of pain medication and red blood cell transfusions in their definition of a severe VOE, these treatments are assumed to be included in standard practices.

Table 3.3. Definitions of Primary Study Outcomes

	exa-cel CLIMB-121[41]	lovo-cel HGB 206[38]
VOC/VOE	Not defined/measured in trial	VOE is defined as an episode of acute pain with no medically determined cause other than a vaso-occlusion and included acute episodes of pain, ACS, acute hepatic sequestration, acute splenic sequestration, and acute priapism
Severe VOC/VOE	Severe VOC is defined as any one of the following: • Acute pain event that requires a visit to a medical facility and administration of pain medications (opioids or IV NSAIDs) or RBC transfusions • ACS, as indicated by presence of new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever • Priapism lasting >2 hours • Splenic sequestration	Severe VOE is defined as any one of the following: • A visit to a hospital or ED that exceeded 24 hours • At least 2 visits to day unit or ED during a 72-hour period (with both visits requiring IV treatment) • Priapism episode lasting more than 2 hours and leading to a medical-facility visit

ACS: acute chest syndrome, ED: emergency department, IV: intravenous, NSAID: non-steroidal anti-inflammatory drug, RBC: red blood cell, VOC: vaso-occlusive crisis, VOE: vaso-occlusive event

lovo-cel

Frequency of Vaso-Occlusion/Pain Events

The primary efficacy endpoint of HGB-206 was the proportion of Group C trial participants who achieved complete resolution of VOEs between six and 18 months after lovo-cel infusion. In an unplanned interim analysis of HGB-206 trial data using a data cut-off of February 2021, nine of 10 trial participants (90%) were VOE-free between six and 18 months of follow-up (Table 3.4). Patients experienced a reduction in the annualized rate of VOEs, from a median baseline of four VOEs (min-max: 2 to 14.5) to zero (0 to 5.9) post-infusion (see Supplement Table D7).

Patients were also assessed for the resolution of *severe* VOEs: an episode of pain requiring a visit to a medical facility. A more recent analysis of the HGB-206 Group C cohort that used a data cut-off date of August 2022 demonstrated that 30 of 31 patients (96.8%) of trial participants were free of severe VOEs between six and 18 months of follow-up.[39] The median annualized rate of severe VOEs was reduced from a baseline of three (min-max: 0.5 to 13.5) to zero (0 to 0.5).

Academic-in-confidence data was provided by the manufacturer on other related outcomes of pain; the average number of annualized hospital days and hospital admissions among Group C trial participants was reduced at 24 months post-infusion (data on file).

Table 3.4. Key Trial Results of lovo-cel (HGB-206 Group C)

Outcomes		N	HGB-206
Number of Participants Achieving Complete Resolution of VOEs Between 6 Months and 18 Months After Drug Product Infusion, n (%)		10*	9 (90)
Number of Participants Achieving Complete Resolution of Severe VOEs, Between 6 Months and 18 Months After Drug Product Infusion, n (%)		31	30 (96.8)
Time to Neutrophil Engraftment, Median (Range) Days		35	20 (12-35)
Time to Platelet Engraftment, Median (Range) Days		35	36 (18-136)
Total Hb Level, Median g/dL	**At Baseline**	22	8.5
	At 6 Months	32	11.5
	At 12 Months	31	12
	At 18 Months	22	12.1
	At 24 Months	16	11.7
Hb^{AT87Q} Fraction in Non-Transfused Total Hb, Median %	**At 6 Months**	32	47
	At 12 Months	31	45
	At 18 Months	22	44
	At 24 Months	16	45

d: deciliter, g: gram, Hb: hemoglobin, n: number, N: total number, VOE: vaso-occlusive event

*The denominator of this proportion was calculated using data from the interim analysis of Group C participants in Figure 3B of the Kanter et al. NEJM publication.[38] At the time of analysis (data cut-off February 17, 2021), only 10 participants had reached a post-infusion follow-up time of 18 months.

Additional Patient-Important Outcomes

Group C HGB-206 trial participants were assessed for improvements in quality of life across three measures: the PRO Measurement Information System-57, pain intensity numeric rating scale, and the EuroQoL-5D-3L Health Utility Index. These instruments are described in greater detail in Supplement A1.

Analysis of PRO Measurement Information System-57 and pain intensity numeric rating scale outcomes was limited to 25 Group C participants who had a follow-up of up to 24 months (see Supplement Table D9).[42] There was a mean improvement at last follow-up in all domains except for anxiety.

Data on the EuroQol-5D-3L Health Utility Index was provided in confidence by bluebird bio for Group C HGB-206 trial participants ages 16 and up; there was an increase in the mean Index at 24 months post-transplant compared to baseline (data on file).

The impact of lovo-cel on Group C HGB-206 trial participants' employment was assessed using the Work Productivity and Activity Impairment Questionnaire: General Health; the number of work hours missed due to health problems and total number of weekly work hours were improved from baseline throughout 36 months of follow-up (data on file).

The lovo-cel clinical development program did not measure several patient-important outcomes identified in our scope (see Supplement D1): cardiovascular events, hearing or vision loss, pregnancy complications, and sexual dysfunction. Organ damage, cognitive functioning, caregiver burden, and infertility have not yet been reported.

Hematological Response

All patients in the Group C cohort of HGB-206 successfully achieved neutrophil and platelet engraftment at a median of 20 and 36 days, respectively (Table 3.4). Trial participants experienced an increase in total hemoglobin levels from a median baseline of 8.5 gram per deciliter (g/dL) to greater than 11 g/dL through 24 months of follow-up. See Supplement Table D7 for more detailed outcomes.

HbS is an abnormal hemoglobin type that distorts the shape of red blood cells (sickle shaped), causing a blockage of blood flow and subsequent clinical complications. Levels of HbS as a percentage of all non-transfused hemoglobin were maintained at a level of approximately 50% post-infusion of lovo-cel from month three throughout month 24; unfortunately, the baseline percentage of HbS of trial participants is unknown and thus the exact suppressive effect of lovo-cel on HbS levels is uncertain.

HbA^{T87Q} is a modified adult hemoglobin with anti-sickling properties; after infusion of lovo-cel, the median percentage of HbA^{T87Q} was greater than 40% of all non-transfused hemoglobin by month three and was sustained throughout 24 months of follow-up.[43] Expression of HbA^{T87Q} at a level of 20-30% is hypothesized to meet the minimum threshold of preventing clinical manifestations and complications of SCD.[43] As of February 2021, an average of 85% of red cells contained HbA^{T87Q} by 24 months (n=10).[38]

In the interim analysis of Group C HGB-206 trial data, four markers of hemolysis (the breakdown of red blood cells) were reported (reticulocyte count, and levels of haptoglobin, lactate dehydrogenase, and total bilirubin) and generally showed a trend towards normalization, approaching levels observed in a healthy population.[38]

exa-cel

Frequency of Vaso-Occlusion/Pain Events

The primary efficacy endpoint of CLIMB-121 was the proportion of participants who had not experienced any severe VOCs for at least 12 consecutive months; this was measured from 60 days after a person's last red blood cell transfusion. Of the 35 enrolled participants, 17 participants were evaluable for the primary endpoint. This cohort experienced an average of 4.6 severe VOCs per year over the two-year period prior to informed consent.[44]

After exa-cel infusion, 16 of the 17 participants (94.1%) remained severe VOC-free for greater than 12 consecutive months. One member of this cohort experienced four severe VOCs over a two-month period; they had a baseline annual rate of three severe VOCs with a prior history of chronic pain and other comorbidities. Of note, a participant who had met the primary efficacy endpoint later experienced a severe VOC in the setting of parvovirus infection. All 17 participants achieved freedom from in-patient hospitalization for severe VOCs for greater than 12 consecutive months. [44]

Table 3.5. Key Trial Results of exa-cel

CLIMB-121			
Outcome	**Timepoint**	**N**	**Exa-cel**
Number of participants who have not experienced any severe VOCs for at least 12 consecutive months, n (%)	From 60 days after last RBC transfusion up to 2 years after exa-cel infusion	17	16 (94.1)
Number of participants free from in-patient hospitalizations for severe VOCs for ≥12 consecutive months, n (%)	From 60 days after last RBC transfusion up to 2 years after exa-cel infusion	17	17 (100)
Proportion of HbF against total Hb, mean %	Baseline	35	*4.8**
	3 months	34	36.8
	6 months	29	*42.4**
	12 months	17	*42.7**
	18 months	12	*41.9**
	24 months	4	*43.2**
Total Hb level, mean g/dL	Baseline	30	9.1†
	3 months	25	12.1†
	6 months	17	12.7†
	9 months	15	13.3†
	12 months	9	12.5†
	15 months	6	13.7†

dL: deciliter, g: gram, Hb: hemoglobin, HbF: fetal hemoglobin, n: number, N: total number, RBC: red blood cell, VOC: vaso-occlusive crisis

*Data have been digitized

†Data are from an earlier cut-off date of February 2022

Additional Patient-Important Outcomes

Three patient-important outcomes were reported for the primary efficacy set (N=17) at the September 2022 data cut-off: the EuroQoL Visual Analog Scale (EQ VAS), the functional assessment of cancer therapy – general (FACT-G), and the bone marrow transplantation subscale of the FACT scale (BMT). Further detail on these scales can be found in Supplement Section A1. The mean change from baseline in all three outcomes met the minimum clinically important difference (MCID)

thresholds at month six and were sustained throughout 18 months of follow-up (See Supplement Table D10).[44-48]

We are aware that quality of life measures including a weekly pain scale, EQ-5D-Youth scale, adult sickle cell quality-of-life measurement system, pediatric quality-of-life inventory, and pediatric quality-of-life SCD module are being measured in the CLIMB-121 trial but the data are not publicly available at this time.

We also set out to look for additional patient-important outcomes outlined in our scope, but we did not identify data on chronic pain, fatigue, cognitive effects, mental health effects (e.g., depression, anxiety), cardiovascular events, hearing or vision loss, organ damage, infertility and pregnancy complications, sexual dysfunction, or ability to work or attend school.

Hematological Response

All patients had successful neutrophil and platelet engraftment at a median of 27 (range: 15-40) and 33 (range: 23-81) days, respectively. The mean time to last red blood cell transfusion was 22.5 days.[44]

Hemoglobin levels were assessed in the study population using an earlier data cut-off of February 2022 (see Table 3.5). At three months, the mean hemoglobin level reached 12.1 g/dL, an increase from a baseline of 9.1 g/dL, and was maintained at a level greater than 11.0 g/dL throughout follow-up. A drop in the mean total Hb levels was observed beyond month 15; however, there is high uncertainty in this waning effect due to the limited follow-up and low number of participants available at later time points.[40] (see Supplement Table D8)

BCL11A is a transcription factor that suppresses fetal hemoglobin in adult cells and editing BCL11A results in increased expression of fetal hemoglobin.[49] Durable BCL11A editing was observed in both the peripheral blood (nucleated cells) and the bone marrow (CD34+ cells) of trial participants.[44]

Patients had clinically meaningful increases in fetal hemoglobin, defined by an absolute increase to >30%, a threshold that has been hypothesized as a curative target.[50-52] Fetal hemoglobin accounted for approximately five percent of the overall hemoglobin at baseline; the mean proportion of fetal hemoglobin reached the 30% threshold by month three and was maintained through 24 months of follow-up. (see Table 3.5)[40] Fetal hemoglobin was distributed equally across red blood cells, reaching greater than 95% distribution by month six; an F-cell distribution of >70% is ideal.[44,53] However, to date, hemolysis data have not been presented and this was considered by clinical experts to be a key component of understanding the clinical relevance of fetal hemoglobin levels.

Harms

lovo-cel

All patients in the Group C cohort of HGB-206 experienced at least one adverse event following lovo-cel infusion, many of which were consistent with background SCD and expected events associated with ASCT and myeloablative conditioning. More than half of Group C participants experienced a grade ≥3 adverse event of stomatitis, thrombocytopenia, and neutropenia (see Supplement Table D11).

One case of a grade 2 febrile neutropenia was deemed by investigators to be related to lovo-cel infusion; two other adverse events (one grade 2 leukopenia and one grade 1 decreased diastolic blood pressure) were deemed to be possibly treatment-related. All three safety events were resolved within a week of onset.

One death occurred in the HGB-206 Group C cohort; a 27-year-old trial participant with severe baseline SCD (29 VOEs in two years prior to trial enrollment) and cardiopulmonary disease experienced a cardiac arrest at 20 months after lovo-cel infusion.[38] This death was attributed to cardiac fibrosis and other chronic cardiopulmonary organ injury and deemed to be unrelated to lovo-cel treatment. Two deaths in an earlier HGB-206 cohort are outlined in greater detail below.

Additional Safety Concerns

Of note are two instances in which the FDA placed a clinical hold on the lovo-cel clinical development program due to safety concerns of hematologic malignancies and persistent anemia.

Myelodysplastic syndrome and acute myeloid leukemia are two hematological malignancies that can develop from abnormal blood cell production in the bone marrow. Patients with SCD have an increased risk of developing both myelodysplastic syndrome and acute myeloid leukemia compared to the general population, even outside of myeloablative transplant settings.[54,55] The risk of developing these diseases may also be associated with gene therapy with γ-retroviral vectors and myeloablation with an alkylating agent.[56]

In February of 2021, bluebird bio announced a complete clinical hold of trials HGB-206 and HGB-210 due to an observed instance of acute myeloid leukemia in a Group A HGB-206 participant.[57,58] This patient had an initial diagnosis of myelodysplastic syndrome at the age of 31, approximately 5.5 years after lovo-cel infusion, and later died from complications of progressive acute myeloid leukemia.[59]

Prior to this clinical hold, another Group A HGB-206 trial participant was diagnosed with acute myeloid leukemia in 2018 after an initial diagnosis of myelodysplastic syndrome three years after

lovo-cel infusion; this patient was 42 years old at trial consent.[56] This case of acute myeloid leukemia was also fatal.[57]

Both cases of acute myeloid leukemia were hypothesized to be related to the baseline risks of SCD and inherent risks of myeloablative conditioning associated with the gene therapy.[59-61] It is important to underscore that although the malignancies were not due to genetic manipulation, chemotherapy and myeloablation is a required precursor to the receipt of gene therapy. This clinical hold was lifted in June of 2021.[62]

In December of 2021, a partial hold was placed on enrollment of patients under 18 into lovo-cel trials due to the potential occurrence of myelodysplastic syndrome in two patients (one adolescent, one adult) in the Group C cohort.[63,64] Both diagnoses of myelodysplastic syndrome were later revised to persistent anemia.[38] Both participants were found to have two α-globin deletions (−α3.7/−α3.7); this alpha thalassemia mutation is hypothesized by bluebird bio to have been the cause of the anemia and has been added to study exclusion criteria for ongoing trials.[39,63] The partial clinical hold was lifted in December of 2022.[65]

exa-cel

The short median follow-up (11.6 months; range: 2.0-39.1) of patients in CLIMB-121 adds uncertainty and precludes us from making a comprehensive review of the safety profile of exa-cel. All patients reported adverse events related to busulfan conditioning and 12 patients (34.3%) reported adverse events related to exa-cel treatment. Serious adverse events were reported in 14 patients (40%). Notable adverse events were febrile neutropenia (51.4%) and reduction in platelet count (54.3%). Additional reporting of adverse events can be found in Supplement Table D12. There were no reported malignancies, though follow-up time is limited.[44] One patient presented with pneumonia and respiratory failure; this resulted in death and investigators attributed it to a SARS-CoV-2 infection and potentially related to a busulfan lung injury.[44] We learned during our scoping phase that at least one patient treated with exa-cel received therapeutic phlebotomy to reduce hemoglobin levels.

exa-cel in Other Populations

Because of limited data, we also reviewed the safety profile of exa-cel in other populations. The CLIMB THAL-111 trial, which evaluated the safety and efficacy of exa-cel in patients with transfusion-dependent beta thalassemia (n=48), reported two patients (4.5%) with serious adverse events related to exa-cel. One patient reported three serious adverse events (hemophagocytic lymphohistiocytosis, acute respiratory distress syndrome, and headache) related to exa-cel treatment and idiopathic pneumonia related to busulfan conditioning. The other patient experienced delayed neutrophil engraftment and thrombocytopenia following the intervention (i.e., conditioning and exa-cel). All serious adverse events were resolved.[44]

Subgroup Analyses and Heterogeneity

Limited trial sample size prevented evaluation of the heterogeneity of treatment effect based on age, genotype, or other factors.

Uncertainty and Controversies

The small sample sizes of the trials of lovo-cel and exa-cel creates uncertainty around the estimates of some of the clinical outcomes, including both efficacy and safety. Given the magnitude of the benefit (e.g., proportion of patients free of VOCs/VOEs) observed for both therapies across the trials, there is high certainty that gene therapies are frequently successful in treating SCD at least in the short run. It is less certain how these therapies will perform in a real world setting and specifically how those therapies might generalize to a broader population beyond the eligibility criteria of a clinical trial. Generalizability outside of the trial setting was a concern raised by clinical experts who estimated that only small proportion (<15%) of people living with severe SCD might satisfy trial criteria.

However, there is much more uncertainty around significant harms such as myelodysplastic events and even mortality. Even though the trials had few participants, two serious hematologic malignancies (both resulting in death) occurred in the trials of lovo-cel and there was one death in the exa-cel trial (attributed to chemotherapy related lung injury and COVID-19). The former is thought not to be due to mutations from the gene therapy itself, but rather the risks of myeloablative chemotherapy in a higher risk patient population. Across all populations, the risk of the chemotherapeutic condition confers some risk of mortality. In addition, clinical experts told us that the risk of malignancy following chemotherapy may be higher in patients with SCD. Other adverse events such as infertility may require years to formally assess, but infertility is known to be a common and nearly ubiquitous consequence of myeloablative chemotherapy. Lastly, adverse events often occur more frequently when a therapy is used outside the careful monitoring of a clinical trial.

There is evidence with lovo-cel that some patients continued to have episodes of acute pain during follow-up and it is likely that trials of exa-cel will observe similar treatment response when more participants achieve follow-up milestones. It is also unlikely that gene therapy will modify existing chronic complications (e.g., kidney disease, chronic pain from avascular necrosis). In addition to a small sample, the length of follow-up translates into uncertainty of the durability of treatment effect. Gene therapy experts told us that long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect.

The trials of lovo-cel and exa-cel compared patients after treatment to their results at baseline. They were not directly compared to each other or to curative treatment with allogenic HSCT. Although trials only included patients who were unable to undergo sibling-matched allogenic HSCT,

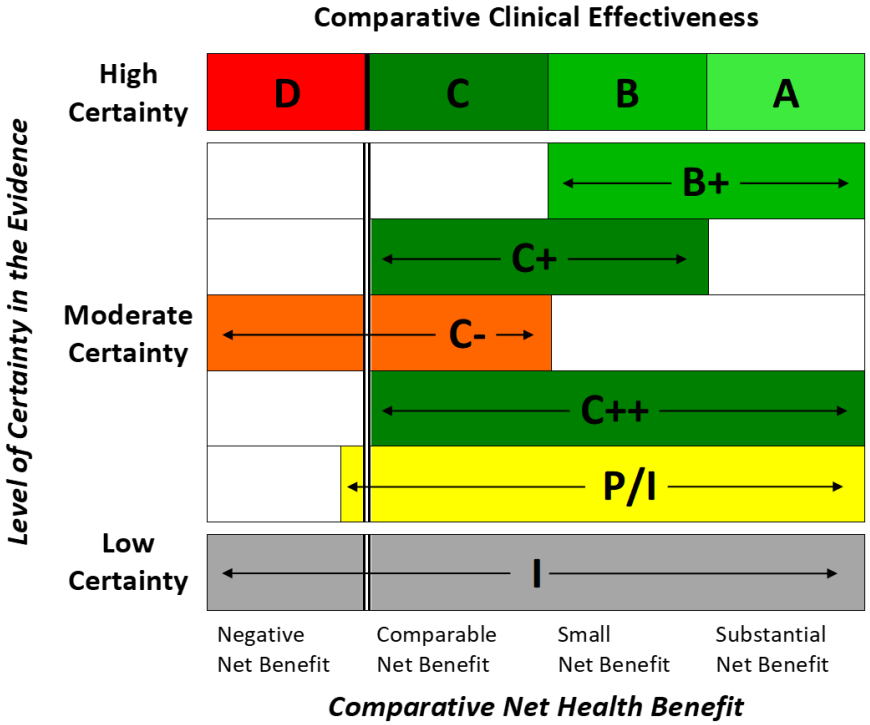
it is uncertain whether clinicians and patients will routinely prefer HSCT in patients with a matched sibling donor.

The two gene therapies have substantially different mechanisms of action. Differences in the definitions of outcomes (VOEs versus VOCs, severe versus non-severe), reporting of data, and small differences in the enrolled trial population make head-to-head comparisons difficult.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



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

Given the marked improvement seen with lovo-cel in a small number of patients with severe SCD and the experience with essentially the same gene therapy in beta thalassemia, we have high certainty that there are substantial short-term improvements in clinical symptoms in the vast majority of patients treated. We have uncertainties about the duration of benefit and the frequency of severe harms that have occurred with myeloablative conditioning as well as theoretical less frequent harms such as insertional oncogenesis from the gene insertion itself. Given the severity of disease in the patients being considered for treatment and the rate of treatment success, we think that despite uncertainties around durability and harms, lovo-cel

provides at least an incremental net benefit compared with standard of care and may provide a substantial net health benefit. For treatment of severe SCD, we rate lovo-cel compared with standard of care as "Incremental or Better" (B+).

Exa-cel presents similar concerns around duration of benefit and harms including those due to myeloablative conditioning and oncogenesis from CRISPR. Although patients treated with exa-cel experienced resolution of severe VOCs, the small sample size leads to uncertainty around what the success rate would be in a larger, real-world, population. In addition, once approved by the FDA, exa-cel would be the first CRISPR therapy. Given these factors, we feel that compared with standard of care, treatment with exa-cel may be comparable, result in incremental net benefit, or result in substantial net benefit. For treatment of severe SCD, we rate exa-cel compared with standard of care as "Comparable or Better" (C++).

Comparison of the therapies to each other is made difficult by the issues raised above around sample size and duration, the different mechanisms of action, and the even more limited experience with CRISPR in humans than with lentiviral gene therapies. Comparing lovo-cel with exa-cel, we rate the evidence as "Insufficient" (I).

Table 3.6. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adolescents and Adults with Severe SCD		
lovo-cel	Standard of care (e.g., hydroxyurea, chronic blood transfusions, pain medication, iron chelation)	B+: Incremental or Better
exa-cel	Standard of care (e.g., hydroxyurea, chronic blood transfusions, pain medication, iron chelation)	C++: Comparable or Better
lovo-cel	exa-cel	I: Insufficient

SCD: sickle cell disease

CTAF Votes

Table 3.7. CTAF Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
Given the currently available evidence, is the evidence adequate to demonstrate that the net health benefit of exagamglogene autotemcel (exa-cel) is superior to that provided by standard of care (i.e., hydroxyurea, chronic blood transfusions, pain medication, iron chelation)?	13	1
Given the currently available evidence, is the evidence adequate to demonstrate that the net health benefit of lovotibeglogene autotemcel (lovo-cel) is superior to that provided by standard of care (i.e., hydroxyurea, chronic blood transfusions, pain medication, iron chelation)?	13	1
Given the currently available evidence, is the evidence adequate to distinguish the net health benefit between exa-cel and lovo-cel?	0	14

The majority of the panel voted that the evidence is adequate to demonstrate that the net health benefit of exa-cel is superior to that provided by standard of care. Panel members turned to the clinical experts with questions about potential barriers to access to exa-cel versus barriers to accessing current standard of care. Clinical experts mentioned that with current available treatments, there is already limited access and treatment options, and feel that the current data for exa-cel is convincing enough to offer ex-cel as a treatment option if approved.

The majority of the panel voted that the evidence is adequate to demonstrate that the net health benefit of lovo-cel is superior to that provided by standard of care. Panel members discussed that while some could argue that it is worth the wait to see more long term evidence from these trials in more patients, the symptoms of sickle cell disease are so severe that the current evidence from the lovo-cel trials appear to provide enough insight its health benefits.

The entire panel voted that there is not enough available evidence to distinguish the net health benefit between exa-cel and lovo-cel.

4. Long-Term Cost Effectiveness

4.1. Methods Overview

The primary aim of this analysis was to estimate the lifetime cost effectiveness of lovo-cel and exa-cel for eligible patients with severe SCD using decision-analytic modeling. As stated in the revised scope, the population of focus 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 VOCs in each of the prior two years.

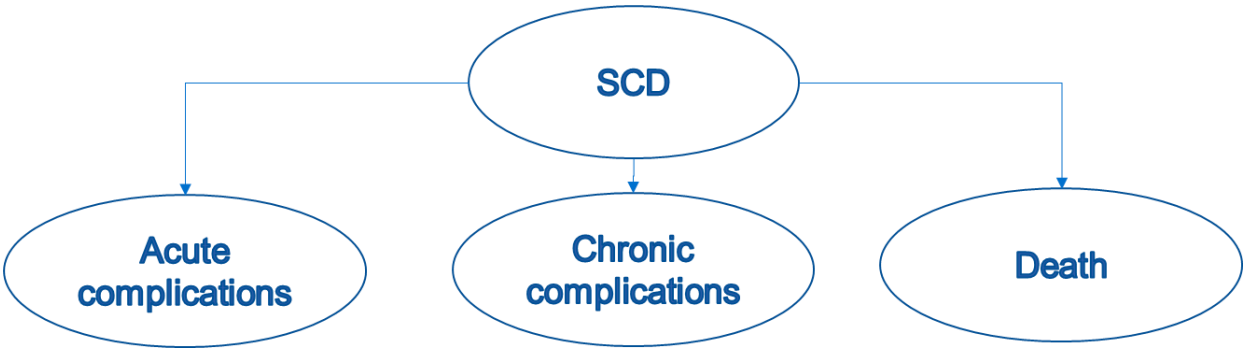
A *de novo* Markov model was developed in Microsoft Excel 2016 to compare each treatment to standard of care using a lifetime horizon. The model estimates outcomes that include life years gained, quality-adjusted life years (QALYs) gained, equal-value life years (evLY) gained, SCD complications, VOCs avoided, and total costs for each intervention over a lifetime time horizon. All costs and outcomes were discounted at 3% per year. Consistent with our prior SCD assessment, we used a co-base case that takes a health care sector perspective (i.e., focuses on direct medical care costs only) as well as a modified societal perspective that also includes productivity changes and caregiver costs (see Supplement Table E1 for an inventory of items included in the health care sector and modified societal perspective analyses). We took a co-base case as the societal costs of care for SCD are large relative to the direct health care costs and the impact of treatment on these costs is substantial (i.e., there are substantial differences in the cost-effectiveness findings between the two perspectives). In this case, the incremental cost-effectiveness ratio from the two perspectives changes by greater than 20% for both of these therapies. Also, as in the clinical evidence review, the comparative value analyses followed the Single and Short-Term Treatment Value Framework adaptations including the addition of the conservative and optimistic scenarios as well as the shared savings analyses.

The model (Figure 4.1) focused on an intention-to-treat analysis with a hypothetical cohort of patients with severe SCD entering the model. Model cycle length was one year, based on what was observed in prior published economic models/clinical data. The model focused on key acute and chronic complications as well as risk of death. The acute and chronic complications considered in the model are listed in Table 4.1. Age-dependent annual probabilities were used to estimate the proportion of patients with acute and chronic complications each year. Patients remained in the model until death, and the patients transitioned to death based on age-dependent annual mortality probabilities. All complications were modeled independently of each other. Treatments that avoid or reduce acute and chronic complications will improve patients' health and may reduce health care costs. Evidence for avoidance or reduction of VOCs was sourced directly from the trials.[1,2] As there is no direct evidence of avoidance or reduction of acute and chronic complications from the trials,

trial data on VOCs and other supporting outcomes was used to estimate the treatment effect on these complications.

Based on the feedback received on the draft report, the number of VOCs per year in the model were changed to 5.1 per year for patients on standard care (rather than the four VOCs per year used in the draft report). This evidence-informed update uses a standard care VOC rate above what was observed in the trial baseline periods but is supported by other observational literature.[66] Given that VOCs in real practice are treated with a wide range of health care resource utilization intensity, increasing the annualized standard care VOC rate while not updating the draft report VOC unit cost is consistent with a best available evidence approach.

Figure 4.1. Model Structure



SCD: sickle cell disease

Table 4.1. Acute and Chronic Conditions Included in the Model

Acute	Chronic
VOCs	Avascular necrosis
Acute chest syndrome	Chronic kidney disease
Acute infections (bacteremia and sepsis)	Heart failure
Acute kidney injury	Liver complications
Gallstones	Pulmonary hypertension
Leg ulcers	Retinopathy
Pulmonary embolism	Chronic lung disease
Stroke	Neurocognitive impairment
Myocardial infarction	Pain and fatigue
	Post-stroke

VOC: vaso-occlusive crisis

4.2. Key Model Assumptions and Inputs

Below is a list of key model choices:

- **Model framework**: We chose a cohort-level *de novo* Markov model rather than a patient-level simulation after consultation with stakeholders. The cohort-level model is appropriate for incorporating the available evidence and allows flexibility in exploring different scenarios.
- **Population**: In the base-case analysis, the model used patient characteristics similar to patients with severe SCD enrolled in Medicaid, and the population was categorized into adolescents and adults.

- **Comparator**: We chose to focus on standard of care as the comparator. We did not include HSCT as a comparator in the model as HSCT is expected to be prioritized in cases where a matched sibling donor is available.
- **Treatment effectiveness**: After feedback on the model analysis plan, we chose to anchor successful gene therapy treatment effectiveness for acute, chronic, and mortality events based on general population rates as well as rates for people with SCD who experience no VOCs. Details are provided below, but generally, all complication and mortality rates for all modeled ages are no lower than the US general population rates but are no higher than rates for people with SCD who experience no VOCs. For acute events and for all events modeled for the adolescent subpopulation, the modeled rates for successful gene therapy were below those observed for people with SCD who experience no VOCs. For chronic events and mortality after successful gene therapy for adults were assumed to be consistent with people with SCD who experience no or limited VOCs.

Our model included several assumptions stated on the following page in Table 4.2.

Table 4.2. Key Model Assumptions

Assumption	Rationale
A proportion of patients were assumed to die in the first model cycle due to the acute risk associated with transplant.	The model included a 1.4% risk of death from infusion work for gene therapy in line with ICER's beta thalassemia report,[67] and this value was tested in sensitivity and scenario analyses
Costs for patients who start the process of pre-transplant assessments and preparation but do not proceed with treatment are included in the model.	Preparation for transplant (e.g., assessments, tests, visits) incur additional costs that should be accounted for in the model.
The model included an evidence-based estimate of treatment failure in the first model cycle.	Where the trial data shows a proportion of patients still with VOCs after treatment, this is modeled assuming that these patients have the same rate of complications and mortality as those on standard care.

Assumption	Rationale
After year seven, patients on both gene therapies revert to costs and outcomes of standard care at a rate used in ICER's beta thalassemia report[67]	The long-term durability of treatment effect is unknown. The uncertainty in the durability of treatment effect was also heard from clinical experts and patient stakeholders.
The cycle length of the model was one year.	Given the chronic nature of SCD, a cycle length of one year is expected to appropriately capture health outcomes and costs and allow for sufficient flexibility to explore our planned sensitivity and scenario analyses.
Some patients have chronic complications at the start of the model.	Some chronic complications will have occurred by the age at the start of the model and the prevalence of these complications were sourced from published literature.
The risk of complications and death in the model were populated using data for Medicaid patients.	While some SCD patients have commercial insurance (with lower risk of complications) or Medicare (with higher risk of complications), most of the SCD patients are covered by Medicaid and, as such, the model was populated using data for Medicaid patients.
All complications (i.e., acute [except VOCs] and chronic) and death were modeled independent of each other.	We used the most relevant robust data sources to model the risk of complications and mortality, which already account for any interdependencies. As the aim is to estimate the cost effectiveness at a population level, this approach is appropriate.
VOC rates are correlated with rates of acute and chronic complications of interest, and mortality.	We used published data on hazard ratios for the complications of interest between SCD patients with zero VOCs and those with 3+ VOCs. Similar approach was also used for mortality rates.
Treatment effect in reducing the VOCs were used to model the impact on risk of complications.	Treatment success was measured as proportion of patients without VOCs, and these patients were modeled with lower risks of acute, chronic complications and mortality.
For chronic complications and mortality, the hazard ratios for adults are different from the adolescents to account for organ damage in the adult population.	Adult patients on SCD are assumed to already accumulate some organ damage before receiving the gene therapy and as such, the treatment effectiveness in reducing chronic complications and mortality is assumed to be lower for adults compared to adolescents (who are less likely to accumulate organ damage).
Health state disutility values were used to estimate QALY losses for acute and chronic complications.	QALY decrements for acute complications were estimated considering the short duration of the disutilities. Chronic complications were assumed to last for lifetime (i.e., until death).
Additive approach was used to estimate the QALYs.	Additive approach was used to estimate the health-related quality of life of patients with multiple complications, to reflect modeling of the complications independently.
For model inputs with no evidence-based specified uncertainty range, we assumed parametric distributions to reflect the uncertainty.	Inclusion of parameter uncertainty within one-way and probabilistic analysis allows for a reasonable characterization of uncertainty.

ICER: Institute for Clinical and Economic Review, QALY: quality-adjusted life year, SCD: sickle cell disease, VOC: vaso-occlusive crisis

Population

The population of focus for the economic evaluation consisted of adolescents and adults with severe SCD, defined as having a minimum of four severe VOCs in each of the two prior years and clinically eligible to undergo bone marrow conditioning and who do not have an HSCT matched donor. In the base case, the model used patient characteristics for Medicaid enrollees with severe SCD as shown in Table 4.3, and the population was categorized into adolescents and adults. Although the proportion of adolescents who chose to receive gene therapy may differ from the assumed proportion (28%), we note that 28% is actually higher than the observed percentage studied in the clinical trials. Given known relationships with evidence, higher proportions of adolescent use, all else being equal, may lead to lower incremental cost-effectiveness findings.

Table 4.3. Baseline Population Characteristics

Baseline Characteristic	Value	Source
Mean Age	20.5 years (SD 6)	Mahesri et al 2022[3]
Proportion Female	54.4%	Mahesri et al 2022[3]
Proportion of Adolescents	28%	Assuming normal distribution (20.5, 6)
Proportion of Adults	72%	Assuming normal distribution (20.5, 6)
Mean Age for Adolescents	15 years	Assuming normal distribution (20.5, 6)
Mean Age for Adults	24 years	Assuming normal distribution (20.5, 6)

SD: standard deviation

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers. The full list of interventions is as follows:

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

Comparator

The comparator for each intervention was standard of care. The incidence rates of complications for patients on standard of care are presented in Supplement E.

Modeling Treatment Effectiveness

The primary measure of clinical efficacy was reduction in VOCs consistent with the key endpoint in the trials, and treatment success was measured as proportion of patients without VOCs. The model included a proportion of patients with treatment failure in the first cycle based on those in the trial that continued to have VOCs after treatment, and these patients were modeled to have the same rate of complications and mortality as those on standard care. The proportion of patients achieving

treatment success was estimated as 96.8% for both therapies, based on the data from the lovo-cel pivotal trial that suggested 30 out of 31 have no further VOCs. Given the smaller sample size in the exa-cel trial, higher uncertainty for exa-cel was reflected in the parametric distribution used for probabilistic sensitivity analysis.

For the patients who do not have any VOCs after gene therapy, hazard ratios were applied to rates of complications for patients on standard care (details are presented in Supplement E). The hazard ratios for death and acute and chronic complications are estimated using the hazard ratios estimated from published literature (for those with zero VOCs versus those with 3+ VOCs) with a multiplier on top to capture the additional benefit of gene therapy treatment. The hazard ratio multipliers are different for death, acute and chronic complications based on the age of treatment (i.e., adolescents or adults). Clinical experts suggested that the patients achieving treatment success on gene therapy are likely to be better than those who had zero VOCs, as such, the hazard ratios estimated from published literature (for patients with zero VOCs versus 3+ VOCs) were multiplied by 0.5 for all patients for acute complications, and adolescents for chronic complications. The hazard ratio multiplier of 0.5 to estimate the hazard ratios for patients achieving treatment success on gene therapy can be considered as being an average of the hazard ratios for the general population (likely to be close to zero) and the hazard ratios of the patients with zero VOCs compared to those with 3+ VOCs. For chronic complications in adults, the hazard ratios were used directly without any adjustment to account for organ damage in the adult population. That is, in the base case, the hazard ratio multipliers for acute complications are 0.5 for both adults and adolescents while for death and chronic complications, the hazard ratio multipliers are 0.5 for adolescents and 1 for adults. In the model, whilst the baseline rates change when adolescents who go on to become adults (i.e., higher baseline rates of complications are applied when they are over 18), the lower hazard ratios are applied throughout the lifetime (i.e., even after they become adults) as they received the gene therapy while they were adolescents.

The long-term durability of treatment effect is unknown, and this uncertainty in the durability of treatment effect was also heard from clinical experts and patient stakeholders. As such, after year seven, patients on both gene therapies revert to costs and outcomes of standard care at the annual rate of 0.27% used in ICER's beta thalassemia report.[9]

Health State Utilities

Health state utilities in the model were populated using data from published literature. A recent systematic review by Jiao et al. 2022 was used to identify the sources that best reflect the utilities for US SCD patients eligible for gene therapy.[12] We used consistent health state utility values across treatments evaluated in the model.

The utility value for uncomplicated SCD (i.e., without any complications) is assumed to be 0.80 based on Anie et al. 2012,[68] in line with the previous ICER report.[13] For intervention-related

disutility, we used disutility estimated based on Matza et al. 2020, which is assumed to last for one year.[14] We included an additional increase in utility of 0.05 for patients without VOCs after gene therapy to account for the reduction in standard of care day-to-day management including those who receive transfusions based on evidence reviewed from stakeholders and evidence or assumptions made from other gene therapy assessments. This additional increase in utility may be considered an optimistic assumption given this additional utility for gene therapies is separate from the utility benefits of reduced VOCs and complications (which are incorporated separately in the model), potentially double counting the utility benefits.

Table 4.4. Health State Utilities

	Utility	Source
SCD Without Complications	0.80	Anie et al. 2012[13]
Disutility Due to Gene Therapy (for 1 Year)	-0.11	Matza et al. 2020[14]
Additional Utility for Patients on Gene Therapy Without VOCs	0.05	Assumption

SCD: sickle cell disease, VOC: vaso-occlusive crisis

Disutilities of complications were sourced from Sullivan et al. 2006[69] as reported in Supplement Table E8. The QALY losses for acute complications were estimated considering their short duration and the QALY losses for chronic complications were estimated assuming they last for lifetime (i.e., until death). An additive approach was used to estimate the QALYs to reflect modeling of the complications independently.

Cost Inputs

All costs used in the model are in 2022 dollars. Details of the costs are presented in Supplement E. For the VOC costs, we used data from Shah et al 2020[70] who report the average cost of VOCs across the different settings (i.e., inpatient, emergency room, outpatient, and office).

Treatment Costs

There are no prices available yet for lovo-cel and exa-cel. As such, a placeholder value of $2 million was assumed based on analyst estimates, pending further discussions with the manufacturers around the price and potential for outcomes-based agreements.

Table 4.5. Treatment Costs

Drug	Anticipated Acquisition Cost*
lovo-cel	$2,000,000
exa-cel	$2,000,000

*Placeholder value based on analyst estimates.

Societal Perspective Inputs

A modified societal perspective is included as a dual base case, using estimates of the cure of SCD on patient productivity and caregiver costs. For patient productivity estimates, we used the proportional decrease in annual median income of 34.1% estimated from Graf et al. 2022[71] (who suggest that patients cured from SCD have an annual salary of $38,618 and having SCD decreased the annual salary to $25,442 as a result of decreased productivity and different earnings trajectory due to SCD-related health crises and hospitalizations, along with decreased life expectancy and decreased opportunity to pursue education) and applied it to the median wage of US population of $56,420.[72] This resulted in annual lost patient productivity of $19,250, which was applied to all adults in the standard of care arm, and these costs were assumed to be eliminated after successful treatment with gene therapy. Some clinical experts suggested that the proposed approach to modeling lost productivity may be optimistic due to lost opportunities to pursue education (for certain adults) as well as other barriers.

For caregiver estimates, we used Holdford et al. 2021 who estimate the annual losses in unpaid work as $19,662 per caregiver.[19,20] Caregiver costs were applied for all adolescents in the standard of care arm, and as above, these costs were assumed to be eliminated after successful treatment with gene therapy.

Model Outcomes

Model outcomes include total life years gained, QALYs gained, evLYs gained, and total costs for each intervention over a lifetime horizon. The model outcomes also include total VOCs as well. Total costs, life years, QALYs, and evLYs gained are reported as discounted values, using a discount rate of 3% per annum (undiscounted results are presented in Supplement E). Incremental analyses report the cost per evLY gained, cost per QALY, and cost per VOC avoided.

Model Analysis

The model estimated the average survival, quality-adjusted survival, drug cost, complication cost, and number of acute complications per patient. Time spent in each health state was summed to provide estimates of life expectancy and quality-adjusted life expectancy. Long-term estimates of costs, QALYs, evLYs gained, and life years were discounted at 3% per year following ICER guidelines, to account for the opportunity cost of current spending and preference for current over future benefits. A more detailed description of evLY calculations can be found in Supplement E.

Cost effectiveness was estimated using the incremental cost-effectiveness ratios (including cost per evLY gained and cost per QALY), with incremental analyses comparing lovo-cel and exa-cel to standard of care. The base-case analysis used a co-base case that takes a health care sector

perspective (i.e., focused on direct medical care costs only) as well as a modified societal perspective that also includes productivity changes and caregiver costs.

Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses were performed by jointly varying all model parameters over the 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We also performed threshold analyses for drug costs across a range of incremental cost-effectiveness ratios ($50,000, $100,000, $150,000, and $200,000 per QALY and evLY gained).

Scenario Analyses

We conducted numerous scenario analyses to assess the robustness of the results across alternative model assumptions and in accordance with the modifications to the ICER value framework for ultra-rare diseases and single and short-term therapies. We include the details and results of scenario analyses below, including the optimistic and conservative benefit scenario, a 50/50 shared savings scenario, and a cost-offset cap scenario. Additional scenario analyses are presented in Supplement E5.

1) A) Optimistic and B) conservative assumptions regarding the benefit of treatment presented in conjunction with the base case.
2) 50/50 shared savings in which 50% of lifetime health care cost offsets from a new treatment are assigned to the health care system instead of being assigned entirely to the new treatment.
3) Cost-offset cap in which health care cost offsets generated by a new treatment are capped at $150,000 per year but are otherwise assigned entirely to the new treatment.

4.3. Results

Base-Case Results

The total discounted costs, VOCs, QALYs, life years, and evLYs over the lifetime time horizon for the health care system perspective and modified societal perspective are detailed in Tables 4.6 and 4.7, respectively.

Table 4.6. Results for the Base Case for lovo-cel Compared to Standard Care

Treatment	Treatment Cost*	Other Costs	Total Cost*	VOCs	QALYs	Life Years	evLYs
Health Care System Perspective							
lovo-cel	$2,000,000	$827,000	$2,827,000	4.18	16.38	21.87	17.31
Standard of Care	--	$1,490,000	$1,490,000	119.26	9.44	15.80	9.44
Modified Societal Perspective							
lovo-cel	$2,000,000	$837,000	$2,837,000	4.18	16.38	21.87	17.31
Standard of Care	--	$1,714,000	$1,714,000	119.26	9.44	15.80	9.44

evLY: equal-value life year, QALY: quality-adjusted life year, VOC: vaso-occlusive crisis

* Placeholder value based on analyst estimates.

Table 4.7. Results for the Base Case for exa-cel Compared to Standard Care

Treatment	Treatment Cost*	Other Costs	Total Cost*	VOCs	QALYs	Life Years	evLYs
Health Care System Perspective							
exa-cel	$2,000,000	$827,000	$2,827,000	4.18	16.38	21.87	17.31
Standard of Care	--	$1,490,000	$1,490,000	119.26	9.44	15.80	9.44
Modified Societal Perspective							
exa-cel	$2,000,000	$837,000	$2,837,000	4.18	16.38	21.87	17.31
Standard of Care	--	$1,714,000	$1,714,000	119.26	9.44	15.80	9.44

evLY: equal-value life year, QALY: quality-adjusted life year, VOC: vaso-occlusive crisis

* Placeholder value based on analyst estimates.

Tables 4.8 and 4.9 present the incremental cost-effectiveness ratios (which include estimates for the incremental cost per QALY gained, incremental cost per life year gained, incremental cost per evLY gained, and incremental cost per VOC averted for the base-case analysis from the health care system perspective and modified societal perspective), for lovo-cel and exa-cel respectively.

Table 4.8. Incremental Cost-Effectiveness Ratios for the Base Case for lovo-cel vs. Standard Care

Treatment	Comparator	Cost per QALY Gained*	Cost per Life Year Gained*	Cost per evLY Gained*	Cost per VOC Averted*
Health Care System Perspective					
lovo-cel	Standard of care	$193,000	$220,000	$170,000	$11,600
Modified Societal Perspective					
lovo-cel	Standard of care	$162,000	$185,000	$143,000	$9,800

evLY: equal-value life year, QALY: quality-adjusted life year, VOC: vaso-occlusive crisis

* Using placeholder price of $2million for lovo-cel based on analyst estimates.

Table 4.9. Incremental Cost-Effectiveness Ratios for the Base Case for exa-cel vs. Standard Care

Treatment	Comparator	Cost per QALY Gained*	Cost per Life Year Gained*	Cost per evLY Gained*	Cost per VOC Averted*
Health Care System Perspective					
exa-cel	Standard of care	$193,000	$220,000	$170,000	$11,600
Modified Societal Perspective					
exa-cel	Standard of care	$162,000	$185,000	$143,000	$9,800

evLY: equal-value life year, QALY: quality-adjusted life year, VOC: vaso-occlusive crisis

* Using placeholder price of $2million for exa-cel based on analyst estimates.

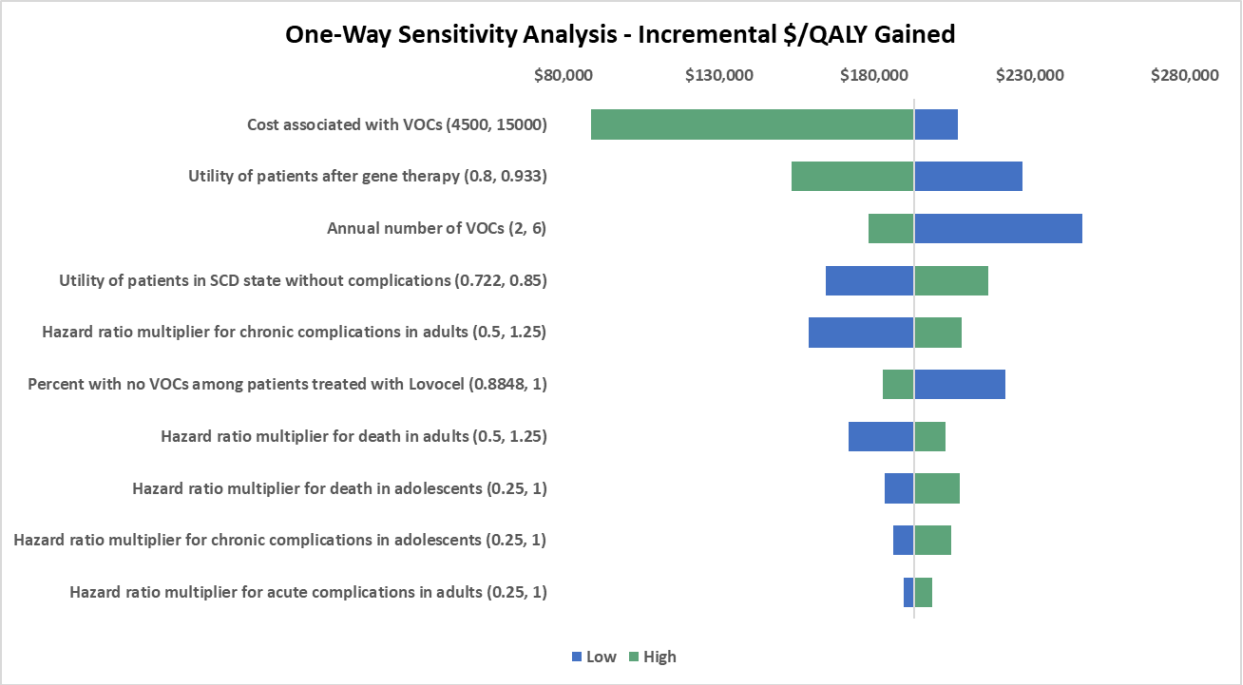
Sensitivity Analyses

To demonstrate the effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors where available or reasonable ranges) to evaluate changes in findings.

We conducted one-way sensitivity analyses to vary one input parameter at a time across its plausible range for the health care system and the modified societal perspective. Figures 4.2 and 4.3 below present this information graphically by way of a tornado diagram for the health care system perspective for lovo-cel and exa-cel, respectively. Sensitivity analysis demonstrates that, for both treatments, the cost of the VOCs, the utility of patients successfully treated with gene therapy, and the annual number of VOCs are the major drivers of cost per QALY (Figures 4.2 and 4.3). In addition, given the greater uncertainty around the treatment success rate of exa-cel due to the small sample size in the exa-cel trial, this was also a major driver of cost per QALY for exa-cel as seen in Figure 4.3.

The hazard ratios for death, acute, and chronic complications are estimated as a hazard ratio estimated from published literature (for those with zero VOCs versus those with 3+ VOCs) with a multiplier added on top to capture the additional benefit of gene therapy treatment. The hazard ratio multipliers are different for death, acute and chronic complications based on the age of treatment (i.e., adolescents or adults). In the base case, the hazard ratio multipliers for acute complications are 0.5 for both adults and adolescents while for death and chronic complications, the hazard ratio multipliers are 0.5 for adolescents and 1 for adults. Given the large number of complications, the hazard ratio multipliers are varied in the one-way sensitivity analysis rather than incorporating all the individual hazard ratio parameters for each of the nine acute complications, 10 chronic complications, and death.

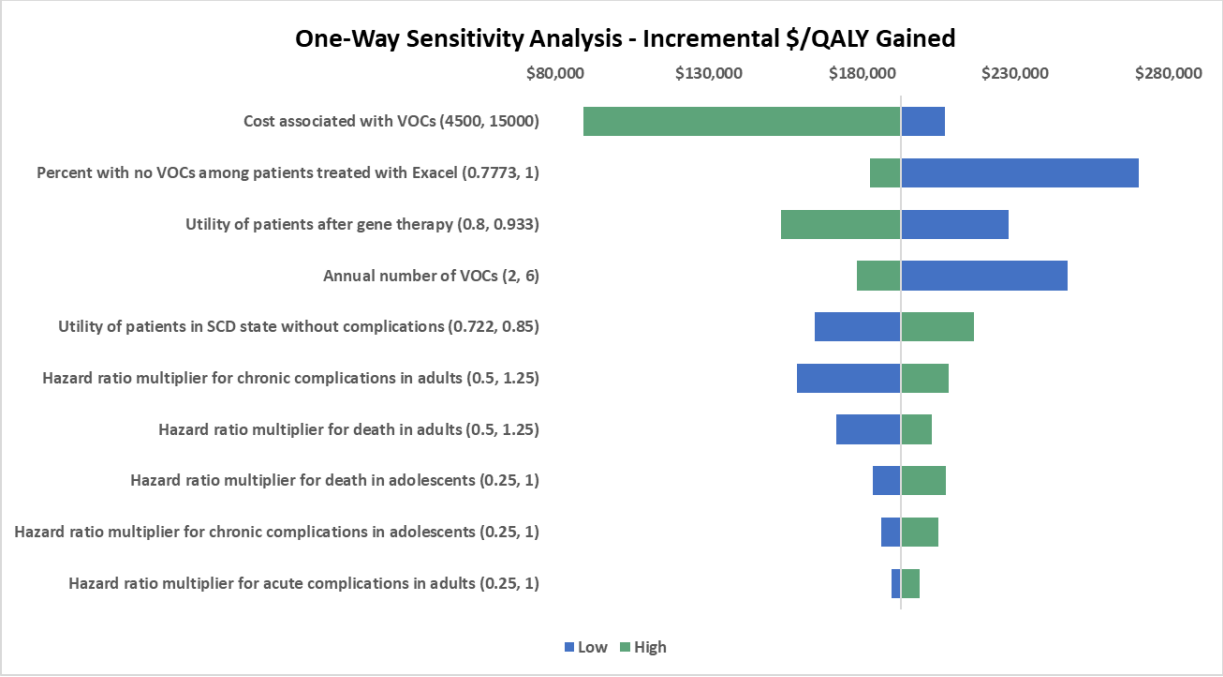
Figure 4.2. Tornado Diagram for lovo-cel (Health Care System Perspective)



QALY: quality-adjusted life year, SCD: sickle cell disease, VOC: vaso-occlusive crisis

* Using Placeholder value price of $2 million for lovo-cel based on analyst estimates.

Figure 4.3. Tornado Diagram for exa-cel (Health Care System Perspective)



QALY: quality-adjusted life year, SCD: sickle cell disease, VOC: vaso-occlusive crisis

* Using Placeholder price of $2 million for exa-cel based on analyst estimates.

A probabilistic sensitivity analysis was conducted to vary all inputs with noted uncertainty simultaneously, and the results are presented in Supplement E. From a health care system perspective, both lovo-cel and exa-cel had 0% probability of being cost effective at a threshold of $150,000 per QALY (and lower) while at a threshold of $200,000 per QALY, lovo-cel had a 29% probability of being cost effective and exa-cel had a 23% probability of being cost effective. When using a modified societal perspective, lovo-cel had 7% probability of being cost effective while it was 5% for exa-cel at a threshold of $150,000 per QALY, and there is a substantial change at a threshold of $200,000 per QALY with an 87% probability of being cost effective for lovo-cel and a 75% probability of being cost effective for exa-cel.

Scenario Analyses

Scenario Analysis 1: Optimistic and Conservative Benefit Scenarios

Optimistic and conservative assumptions regarding the benefit of treatment with lovo-cel or exa-cel were performed to reflect the uncertainty in the clinical data. Details of the scenarios are provided in Supplement E. In the base-case analysis, we chose to anchor successful gene therapy treatment effectiveness for acute, chronic, and mortality events to be between the general population rates and the patients with SCD who experience no VOCs. If the complication and mortality rates in the gene therapy arm are closer to the US general population rates, then the gene therapies are likely to have an incremental cost effectiveness below $150,000 per QALY and $150,000 per evLY gained from the health care system perspective. However, if the complication rates for patients in the gene therapy arm are similar to patients with severe SCD who experience no VOCs, then the gene therapies are likely to have an incremental cost effectiveness above $200,000 per QALY and $200,000 per evLY gained from the health care system perspective.

Table 4.10. Scenario Analysis Results for the Optimistic and Conservative Benefit Scenarios

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per VOC Averted
Health Care System Perspective					
Base Case	Standard of care	$193,000	$220,000	$170,000	$11,600
Optimistic	Standard of care	$138,000	$154,000	$125,000	$10,600
Conservative	Standard of care	$246,000	$261,000	$206,000	$12,300
Modified Societal Perspective					
Base Case	Standard of care	$162,000	$185,000	$143,000	$9,800
Optimistic	Standard of care	$114,000	$127,000	$103,000	$8,700
Conservative	Standard of care	$208,000	$221,000	$175,000	$10,400

evLY: equal value life year, QALY: quality adjusted life years, VOC: vaso-occlusive crisis

* Using placeholder price of $2 million for lovo-cel or exa-cel based on analyst estimates.

Scenario Analysis 2: 50/50 Shared Savings Scenario

A 50/50 shared savings scenario analysis was undertaken in which 50% of lifetime health care and non-health care (for the modified societal perspective) cost offsets from lovo-cel or exa-cel are assigned to the health care system instead of being assigned entirely to the treatment. Results are presented in Table 4.11.

Table 4.11. Scenario Analysis Results for the 50/50 Shared Savings Scenario

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per VOC Averted
Health Care Perspective					
lovo-cel or exa-cel*	Standard of care	$253,000	$289,000	$223,000	$15,200
Modified Societal Perspective					
lovo-cel or exa-cel*	Standard of care	$243,000	$278,000	$214,000	$14,600

evLY: equal-value life year, QALY: quality-adjusted life year, VOC: vaso-occlusive crisis
*Using Placeholder price of $2 million for lovo-cel or exa-cel based on analyst estimates.

Scenario Analysis 3: Cost-Offset Cap Scenario

A cost-offset cap scenario analysis was undertaken in which health care and non-health care (for the modified societal perspective) cost offsets generated are capped at $150,000 per year but are otherwise assigned entirely to the treatment. Cost offsets did not exceed $150,000 in any modeled year; therefore, results are aligned with the base-case findings.

Threshold Analyses

Threshold analyses were conducted to identify at what price lovo-cel or exa-cel would meet certain cost-effectiveness thresholds. Tables 4.12 and 4.13 present the findings from these threshold analyses for the health care system perspective and modified societal perspective using outcomes of both the QALY and evLY, respectively. The prices presented in Table 4.12 do not include costs for workup and preparation, transplant, or post-transplant monitoring costs and therefore represent threshold prices for acquisition alone. We have also estimated threshold based prices assuming simple outcomes based agreements and the results for this scenario are presented in Table E16 of the Supplement.

Table 4.12. QALY-Based Threshold Analysis Results

Treatment	Placeholder Price per Unit*	Unit Price to Achieve $50,000 per QALY Gained	Unit Price to Achieve $100,000 per QALY Gained	Unit Price to Achieve $150,000 per QALY Gained	Unit Price to Achieve $200,000 per QALY Gained
Health Care System Perspective					
lovo-cel or exa-cel	$2,000,000	$1,000,000	$1,350,000	$1,700,000	$2,040,000
Modified Societal Perspective					
lovo-cel or exa-cel	$2,000,000	$1,220,000	$1,570,000	$1,910,000	$2,260,000

QALY: quality-adjusted life year

*Excludes workup and preparation, transplant, or post-transplant monitoring costs. Unit price represents the placeholder value for the full acquisition cost of lovo-cel or exa-cel per patient.

Table 4.13. evLY-Based Threshold Analysis Results

Treatment	Placeholder Price per Unit*	Unit Price to Achieve $50,000 per evLY Gained	Unit Price to Achieve $100,000 per evLY Gained	Unit Price to Achieve $150,000 per evLY Gained	Unit Price to Achieve $200,000 per evLY Gained
Health Care System Perspective					
lovo-cel or exa-cel	$2,000,000	$1,050,000	$1,440,000	$1,840,000	$2,230,000
Modified Societal Perspective					
lovo-cel or exa-cel	$2,000,000	$1,270,000	$1,660,000	$2,050,000	$2,440,000

evLY: equal-value life year

*Excludes workup and preparation, transplant, or post-transplant monitoring costs. Unit price represents the placeholder value for the full acquisition cost of lovo-cel or exa-cel per patient.

Model Validation

We used several approaches to validate the model. First, we provided preliminary model structure, methods and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we also offered to share the model with the relevant manufacturers for external verification around the time of publishing the draft evidence report for this review. Finally, we compared results to other cost-effectiveness models in this therapy area. The outputs from the model were validated against the trial/study data of the interventions and any relevant observational datasets.

Uncertainty and Controversies

There have been several publications on SCD in the past couple of years, including on the rate of complications,[73-76] costs,[77] utilities,[78] and conceptual modelling,[71,79-81] with a number of them published by the Sickle Cell Clinical and Economic Impact Consortium (including the University of Washington and Fred Hutch Research Center) from their research funded by the National Institutes of Health National Heart, Lung, and Blood Institute. These publications have been instrumental in supporting the development of the cost-effectiveness model as well as assisting to address some of the uncertainties involved in modeling SCD. However, evidence uncertainties remain in estimating a SCD gene therapy's impact on day-to-day quality of life and acute, chronic, and fatal SCD-associated events.

Salcedo et al 2021[71,79-81] estimated the cost effectiveness of a hypothetical single-administration durable treatment for SCD provided at birth, assuming a "fully effective" cure (i.e., no disease-related complications and costs) along with life expectancy and health-related quality of life of general population. Their base-case incremental cost-effectiveness ratio of $140,877 per QALY relative to standard of care, using a one-off cost of $2.1 million for the durable treatment, is lower than that estimated from our cost-effectiveness model. This difference is expected as the durable treatment was assumed to be given at birth (thus accumulating benefits over the whole lifetime) along with the optimistic assumptions around a complete cure in Salcedo et al 2021.[71,79-81]

The population of focus for the assessment is patients living with severe SCD, who are defined as having an average of four VOCs each year in the past two years based on trial evidence. In the model, the patients on standard care were assumed to have 5.1 VOCs per year that required health care use until death (around 119 VOCs over the whole lifetime) while those who were successfully treated with gene therapy were assumed to have no VOCs, which resulted in substantial cost offsets in the treatment arm. The cost per VOC was estimated as $5,762 as the average cost of VOCs across the different (i.e., inpatient, emergency room, outpatient, and office) settings. The use of 5.1 VOCs per year versus four VOCs per year in the model is consistent with observational evidence and a recognition of a wide spectrum of health care utilization used to treat VOCs in real practice. If the number of VOCs or cost per VOC in real practice is lower than the values used in the model, this would result in an increase in the incremental cost-effectiveness ratios of gene therapies compared to standard of care.

Estimating the lifetime health outcomes and costs of gene therapies required assumptions and were conducted under conditions of evidence uncertainty. As shown in the scenario analyses, the cost-effectiveness findings are sensitive to the assumptions around the impact of gene therapies in reducing the complications. After feedback on the model analysis plan, we chose to anchor successful gene therapy treatment effectiveness for acute, chronic, and mortality events to be between the general population rates and the patients with SCD who experience no VOCs. If the

complication and mortality rates in the gene therapy arm are closer to the US general population rates, then the gene therapies are likely to have an incremental cost effectiveness below $150,000 per QALY and $150,000 per evLY gained from the health care system perspective. However, if the complication rates for patients in the gene therapy arm are similar to patients with SCD who experience no VOCs, then the gene therapies are likely to have an incremental cost effectiveness above $200,000 per QALY and $200,000 per evLY gained from the health care system perspective. Also, given there is no known transaction price we can observe for either lovo-cel or exa-cel, we have used a placeholder price of $2 million.

We note that given the increased rate of complications and death with age for patients on standard of care, and the assumptions around treatment effectiveness based on the age at treatment, the population's age will have impact on the cost effectiveness of gene therapies (with all else equal, those of younger age are associated with a lower incremental cost-effectiveness ratio). Although we used a cohort-based model, we did account for known differences between adolescents and adults in costs and outcomes. Because policymaking will remain at the population level, the base-case cost-effectiveness findings and corresponding threshold-based prices presented in this report remain at the population level that average over the eligible population's age.

Additionally, we heard from people living with SCD and their caregivers that some people may not opt for gene therapies, if available and covered under their health benefit, given their preferences and their own risk-benefit tradeoffs. In short, for some people living with SCD, the risks and time invested may not be worth the potential long-run health and other benefits. One major limitation in the cost-effectiveness model is that it assumes risk neutrality in estimating the expected lifetime health gains associated with gene therapies versus standard of care. Therefore, the expected lifetime health gains summarized in this section of the report may be best thought of conditioned on this narrower subpopulation of those who would have considered allogenic HSCT but did not have a matched donor (i.e., those that would consider the net health benefit of opting for gene therapy to be positive). There is strong overlap between a narrower population that may consider gene therapies, if approved, and those who would have considered allogenic HSCT but did not have a matched donor (as like gene therapies, HSCT requires high doses of conditioning chemotherapy and a non-zero risk of short-term death).

As observed in the threshold-based draft price findings, the potential cost savings and health gains are both contributors to the threshold-based draft price justification. The potential cost savings being a factor was also demonstrated by the changes in cost-effectiveness findings to above commonly cited thresholds when assuming a 50/50 cost-savings scenario whereby only 50% of the cost savings were assigned when estimating the cost effectiveness of gene therapies. As highlighted above, the majority of the cost savings are from avoiding VOCs, and if the number of VOCs or cost per VOC in real practice is lower than the values used in the model, this would result in

an increase in the incremental cost-effectiveness ratios of gene therapies compared to standard care.

4.4 Summary and Comment

The analyses suggest that treating eligible patients living with SCD with lovo-cel or exa-cel results in lifetime health gains and added costs when compared to standard of care alone. Patients that were treated successfully experienced large health gains both in length of life and quality of life. When assuming a placeholder price for lovo-cel and exa-cel of $2 million dollars and applying standard 3% per year discounting, these gene therapies have an incremental cost effectiveness that is above commonly cited thresholds from the health care system perspective. Findings from the modified societal perspective that included estimates of productivity loss for patients and caregivers approximate the high end of commonly cited thresholds assuming the $2 million dollar placeholder price. The cost-effectiveness findings were driven by the lifetime opportunity to improve health and reduce VOC-related and other SCD-related costs, and to improve productivity and reduce caregiver costs in the modified societal perspective.

5. Contextual Considerations and Potential Other Benefits

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 was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the interventions in this review.

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	People with SCD are at risk for many acute, severe complications, particularly in setting of VOEs including but not limited to infection, stroke, myocardial infarction, blood clots, and renal infarctions. The complications can lead to significant disability and death.
Magnitude of the lifetime impact on individual patients of the condition being treated	Patients with SCD are born with the condition, often experience their first symptoms during the first year of life and have significant morbidity and mortality even at a young age. The cumulative burden of disease is substantial.

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	If gene therapies effectively cure SCD, it is expected that people will experience increases in quality of life and their ability to achieve major life goals related to education, work, or family life. A negative effect may be the impact of myeloablative condition on fertility and family planning.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	With a clinical cure for SCD, there is a high likelihood that caregivers' ability to return to school and/or work and overall productivity will improve.
Patients' ability to manage and sustain treatment given the complexity of regimen	Curative therapy will reduce the need for other long-term medical therapies (standard of care). However, gene therapies will require patients to be hospitalized for treatment and undergo myeloablative conditioning. Periods of hospitalization can last several weeks and come with potential risks.
Society's goal of reducing health inequities	SCD primarily affects the Black population in the US. It appears that there has been less research into this devastating condition than would have been expected had the disease comparably affected the majority White population. Additionally, people with SCD frequently experience undertreatment for pain in part because of issues around implicit bias and systemic racism. SCD is also a condition that is

	subject to inequity in health care due to racial bias and stigma. While gene therapies do not specifically address implicit bias, stigma, or racism, they represent a long overdue focus on new therapies for vulnerable patients with a high illness burden. We estimated the Health Improvement Distribution Index (HIDI) for Black Americans living with SCD as approaching 7.35. This HIDI score suggests that Black Americans as a subpopulation would benefit more on a relative basis (up to 7.35 times more) from an effective intervention in SCD compared with the overall American population (Supplement A).

CTAF VOTES

At the public meeting, the CTAF deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

When making judgments of overall long-term value for money, what is the relative priority that should be given to *any* effective treatment for Sickle Cell Disease, on the basis of the following contextual considerations:

Table 5.3. CTAF Votes on Contextual Considerations Questions

Contextual Consideration	Very Low Priority	Low priority	Average priority	High priority	Very high priority
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	0	2	3	4	5
Magnitude of the lifetime impact on individual patients of the condition being treated	0	0	0	1	13

Based on perspectives shared by the clinical experts about candidate eligibility for these treatments and the need to receive either exa-cel or lovo-cel before irreversible complications occur, the majority of the council voted that given the acuity of need for treatment of individual patients with SCD, high priority and very high priority should be given to any effective treatment.

After hearing from one patient expert about their positive, life-changing experiences after receiving gene therapy, and another patient expert about their perspectives on the chance for gene therapies to provide a better quality of life, the majority of the council voted that very high priority should be given to any effective treatment based on the magnitude of the lifetime impact on individual patients with SCD.

What are the relative effects of exa-cel/lovo-cel versus standard of care on the following outcomes that inform judgment of the overall long-term value for money of exa-cel/lovo-cel?

5.4. CTAF Votes on Potential Other Benefits or Disadvantages Questions

Potential Other Benefit or Disadvantage	Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
Patients' ability to achieve major life goals related to education, work, or family life	0	0	0	0	14
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	0	2	12
Patients' ability to manage and sustain treatment given the complexity of regimen	0	0	0	4	10
Society's goal of reducing health inequities	0	0	0	4	10

The entire panel voted that exa-cel/lovo-cel would have a major positive effect versus standard of care when considering patients' ability to achieve major life goals related to education, work, or family life. The council considered the experiences of one of the patient experts who described their work life before and after gene therapy and how much more they are now able to do.

Based on the context provided by one patient expert and oral commenters who are caregivers, most members of the council voted that exa-cel/lovo-cel would have a major positive effect versus standard of care when considering caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life.

The council members deliberated after hearing from clinical experts about taking a brief but very intense treatment versus daily adherence to medication. Clinical experts also commented on the importance of having treatment options, as sickle cell disease is a serious disease for everyone with it, and being able to unburden patients from a day-to-day adherence could be beneficial. A council member raised a point about how this may come down to patient preference. Most council members voted that exa-cel/lovo-cel would have a major positive effect versus standard of care when considering patients' ability to manage and sustain treatment given the complexity of regimen, while four voted a minor positive effect.

Patient experts and clinical experts alike commented that they do not think gene therapies, no matter what kind of access is available, can cure racism and that inequalities in our systems will not be solved solely by a new treatment. Similarly, it was discussed how offering an innovative option for therapies such as exa-cel/lovo-cel is one small step, but there is a lot of work to be done to fix the racial inequities that impact people with sickle cell disease. Most of the council voted that exa-cel/lovo-cel versus standard of care would have a major positive effect in society's goal of reducing health inequities, and four members voted a minor positive effect.

6. Health-Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for the annual cost of treatment with lovo-cel or exa-cel are presented in Table 6.1 below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLY gained. For this assessment, the health care system perspective and the modified societal perspective were considered part of a co-base case. Therefore, both perspectives are included. The HBPB for both lovo-cel and exa-cel ranges from $1,350,000 to $2,050,000.

Table 6.1. Annual Cost-Effectiveness Threshold Prices for Lovo-cel and Exa-cel

	Placeholder Price*	Price at $100,000 Threshold	Price at $150,000 Threshold
Health Care Perspective			
QALYs Gained	$2,000,000	$1,350,000	$1,700,000
evLYs Gained	$2,000,000	$1,440,000	$1,840,000
Modified Societal Perspective			
QALYs Gained	$2,000,000	$1,570,000	$1,910,000
evLYs Gained	$2,000,000	$1,660,000	$2,050,000

evLY: equal value life year, QALY: quality-adjusted life year

*Excludes workup and preparation, transplant, or post-transplant monitoring costs. Unit price represents the placeholder value for the full acquisition cost of lovo-cel or exa-cel per patient.

CTAF Votes

Long-term value for money votes were not taken at the public meeting because a net price for lovo-cel or exa-cel was not available.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model from the health care system perspective were used to estimate the potential total budgetary impact of lovo-cel and exa-cel for eligible people with severe SCD. We used a placeholder price of $2 million per treated patient to be paid up front, the same as in the base-case cost-effectiveness analysis, and the three threshold prices (at $50,000, $100,000, and $150,000 per health unit gained) in our estimates of budget impact. For this report version, given that the deterministic cost-effectiveness findings are the same for lovo-cel and exa-cel, we present one set of budget impact findings that may be assigned to either lovo-cel or exa-cel. If numerically different for future versions of this report, findings will be presented by product.

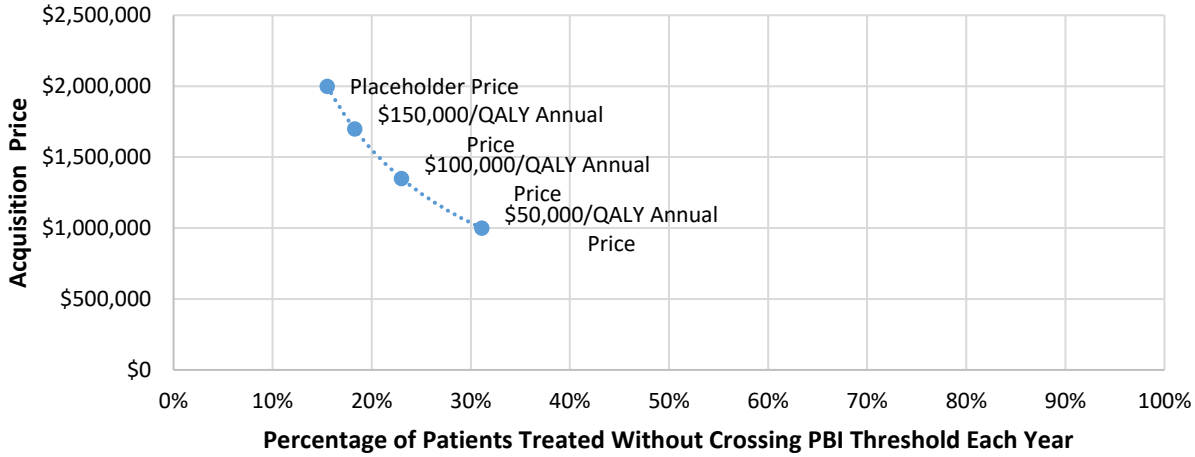
This potential budget impact analysis included the estimated number of people in the US who are likely to be eligible for treatment. We acknowledge that those eligible may be larger than the number of people who may ultimately choose to receive either lovo-cel or exa-cel. Therefore, these results should be interpreted as the potential budget impact rather than a forecast of what might be. To estimate the size of the potential candidate populations for treatment, we used manufacturer data submissions and literature to consider those who are likely to be eligible for lovo-cel or exa-cel to be between 20,000 and 25,000 people living with severe SCD in the US.[82-84] We used the upper end of this range (25,000) and divide this estimate in two for those eligible for lovo-cel (N=12,500) and separately, exa-cel (N=12,500) as per ICER's Reference Case. For the purposes of this analysis, we assume that 20% of these people would initiate treatment in each of the five years, or 2,500 people per year per gene therapy. The aim of the potential budgetary impact analysis is to document the percentage of people who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2022-2023, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $777 million per year for new drugs.

7.2. Results

Results showed that at the placeholder price of $2 million per treatment course for lovo-cel or exa-cel (to be paid up front), 15.5% of people (N=388 people per year) could be treated over the span of five years without crossing the ICER budget impact threshold of $777 million per year. Similarly, 31.1%, 23.0%, and 18.3% could be treated with either lovo-cel or exa-cel without reaching the potential budget impact threshold at the three threshold prices (approximately $1.00 million, $1.35 million, and $1.70 million per treatment) (Figure 7.1).

The cumulative per patient budgetary impact findings using the placeholder acquisition price for lovo-cel or exa-cel are presented in Supplement F.

Figure 7.1. Budgetary Impact of Lovo-cel or Exa-cel in Severe SCD



PBI: potential budget impact, QALY: quality-adjusted life year

Access and Affordability Alert

ICER is not issuing an access and affordability alert for gene therapies for SCD. Although pricing is not yet known for either lovo-cel or exa-cel, we heard from multiple stakeholders that initial uptake of these therapies is unlikely to be rapid. As such, we do not expect that the number of patients treated within five years will result in costs exceeding the ICER potential budget impact threshold of $777 million per year.

The purpose of an ICER access and affordability alert is to signal to stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services, creating pressure on payers to sharply restrict access, or causing rapid growth in health care insurance costs that would threaten sustainable access to high-value care for all patients.

8. Policy Recommendations

Following the CTAF's deliberation on the evidence, a policy roundtable discussion was moderated by ICER's president around how best to apply the evidence on the use of lovo-cel and exa-cel. The policy roundtable members included two patient advocates, two clinical experts, two payers, and two representatives from the drug makers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found here.

All Stakeholders

Recommendation 1

All stakeholders have a responsibility to ensure equitable and optimal patient access to gene therapies for sickle cell disease (SCD) (i.e., lovo-cel and exa-cel).

Stakeholder groups, including patients and clinicians, told us that standards of care for SCD are often sub-optimal and due to a multitude of factors including, but not limited to: stigma, bias, lack of sub-specialists, and transportation. Thus, it is particularly important that all stakeholders take steps to facilitate access to potential cures for SCD in a way that does not exacerbate the health inequities (e.g., by race, geography, health literacy) that characterize the US health care system. But the focus on equitable access should not be isolated to emerging gene therapies. It is likely that gene therapies will only be accessible through Centers of Excellence. Steps should be taken by all stakeholders to ensure that all patients living with SCD have access to multidisciplinary care through these Centers that takes a broad view of the needs of patients and their families for services such as mental health and social support.

Policymakers and life science companies should also note that, while SCD is still considered a rare disease in the US (affecting approximately 100,000 people), the global prevalence and burden of disease with SCD is much higher. Unfortunately, current incentives and business models for innovation will not make it easy for the vast majority of the world to access potentially curative (and life-changing) gene therapies. Lack of global equity in both research and clinical care is an urgent ethical challenge in public health that can only be addressed by all stakeholders working together.

To address these concerns:

<u>Manufacturers should take the following actions:</u>

- Even though potentially curative gene therapies should and will command a high price, pricing still drives many access challenges, and manufacturers should price new gene therapies for SCD at the lower range of cost-effective pricing, particularly during the early years after launch when considerable uncertainty remains regarding the safety and long-term durability of benefits with treatment.

- Manufacturers should work with SCD treatment centers (e.g., Centers of Excellence) and payers to ensure that people living with SCD who are eligible and interested in gene therapy have reasonable access to it, including considerations regarding non-English speaking patients, the need for travel, coverage for ancillary care, and out-of-pocket financial burden.

- If there are geographic regions poorly served by Centers of Excellence, the manufacturer should work with clinical experts, patient advocacy groups, and others to expeditiously expand sites where gene therapy can be obtained.

- Seek to engage with other life science companies and international policymakers to perform industry-wide actions that can make transformative gene therapies available to lower income countries in a fashion that maintains incentives for innovation.

Payers should take the following actions:

- Coverage for gene therapy should be provided in a comprehensive fashion, including coverage for travel, ancillary care pre- and post-procedure (including mental health care), fertility preservation, and out-of-pocket financial burden. All elements must be addressed and aligned in order to reduce the risk that introduction of gene therapies for SCD will create new health equity concerns within a population that has had to bear many years of historical and ongoing discrimination.

Clinical specialty societies should take the following actions:

- Specialty societies should develop evidence-based guidelines and care pathways to help facilitate the delivery of optimal care for SCD. These professional groups should prepare immediately to produce updated guidelines that can guide understanding among payers and others of how to integrate these new treatments into care in an equitable fashion. Stigma, bias, and structural racism still perpetuate sub-optimal care and it is imperative that clinical societies play in role in mitigate their negative impacts.

- Specialty societies should also develop best practices around shared medical decision-making in order to facilitate meaningful patient access to a therapy that has a high likelihood of benefit, but still significant uncertainty around risks. Shared decision-making should also be done in such a way that it does not exacerbate disparities through attention to health literacy and incorporation of cultural competencies into provider trainings and patient-facing materials.

Payers

Recommendation 1

Given that there is insufficient evidence at present to distinguish between the safety or effectiveness of lovo-cel and exa-cel, and that clinical experts see no clinical reasons to favor one of the therapies for certain patient subgroups, payers may consider negotiating a lower price by covering only one of the two therapies. However, payers considering this coverage approach should be aware of important access and patient preference issues that may outweigh the benefit of achieving a lower price.

Although lovo-cel and exa-cel use different methods of gene therapy, if they both receive FDA approval with currently known evidence, there appears to be no clinical reason that both therapies need to be routinely covered if payers wish to negotiate for lower prices by excluding one therapy from coverage. This kind of aggressive formulary management can in some cases produce large reductions in net prices, a cost reduction that would not directly benefit SCD patients but which would contribute to moderating insurance premiums (or tax payments) for the entire health system. Nonetheless, there are important factors that would suggest that payers should opt for covering both therapies. First, it is possible that some SCD Centers of Excellence themselves will decide to offer only one of the therapies, potentially complicating access for patients should their insurance plan not cover the gene therapy provided by their current specialist or the specialist nearest their home. Second, individual patients may have strong preferences for one particular method of gene therapy, with some patients potentially favoring the approach that does not insert new DNA (exa-cel), whereas other patients may prefer the approach with a longer track record (lovo-cel). In this context, sensitivity around patients being "forced" to use only the single approach covered by their insurer should be an important consideration for all payers. Finally, the evidence on these two therapies will be evolving rapidly, heightening the risks that new evidence would quickly render any coverage exclusion obsolete.

Recommendation 2

If the announced prices for lovo-cel and exa-cel align with expected patient benefits and be set toward the lower edge of their estimated cost-effectiveness ranges, payers should use the FDA label as the guide to coverage policy without narrowing coverage by including specific clinical trial restrictions unrelated to the likelihood of benefit from treatment.

Although lovo-cel and exa-cel have strong evidence of substantial *short-term* net health benefit, given the existence of alternative first-line curative therapy for some patients (i.e., HSCT) and uncertainty around longer-term safety and durability, it is reasonable for payers to use prior authorization as a component of coverage. Prior authorization criteria should be based on the FDA label, clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. Coverage for therapies with prices set in fair alignment with the benefits for patients should not be restricted by including requirements not in the FDA label unless these requirements were part of the clinical trial eligibility and are required to assure that patients are not unreasonable candidates for treatment from a clinical perspective. The process for prior authorization should be clear and efficient for providers and patients. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.

Recommendation 3

Since patients will need coverage for therapies that will only be accessible in specific medical centers, payers should design coverage policies that can support travel for patients and their families to receive therapy. Geographical and income constraints should not undermine the tenets of fair access to which all patients have a fundamental right.

Recommendation 4

Payers should cover fertility preservation in concert with coverage of gene therapies. Both patient stakeholders and clinical experts noted that future fertility is a key consideration in management. There are many complex issues regarding fertility (e.g., prepubescent patients, ongoing storage). Payers must be pro-active and transparent about what will be covered.

Manufacturers

Recommendation 1

Manufacturers should align prices with independent estimates of the patient-centered therapeutic value of their treatments, and in the context of significant uncertainty regarding longer-term safety and durability of benefits, prices should be set at the lower end of a reasonable cost-effectiveness range.

New potentially curative therapies for SCD bring the promise of considerable short-term as well as lifetime benefit, but there also remains substantial uncertainty regarding longer-term safety and the durability of benefits. Pricing at launch should reflect the estimated lifetime benefits of treatment, including broader benefits to patients along their life course, but in the context of this heightened uncertainty, manufacturers should seek to price new treatments at the lower range of cost-effective pricing until additional real-world evidence is available.

Recommendation 2

Although equitable access to gene therapy for SCD can improve racial health equity, manufacturers should not inflate pricing to account for this value. If anything, lower pricing will produce fewer access challenges for health systems and patients, and manufacturers should share in the social responsibility to make these treatments available and affordable.

While society gives priority and assigns value to therapies that reduce disparities[85], this value above and beyond the direct health benefits of treatment should not be translated into higher prices and profits for manufacturers. Society's appreciation of the value of reducing disparities should translate into additional funding for at-risk communities themselves.

Recommendation 3

In the context of high-impact single or short-term therapies, transparent consideration should be given to a pricing scenario that "shares" any substantial cost-offset of treatment so that potentially large cost-offsets are not used to justify exceedingly high one-time prices.

Valuing new interventions in reasonable alignment with their added benefits for patients and families is a foundation for affordable access that still retains the necessary incentives for meaningful innovation. However, with potentially transformative single-time therapies, traditional methods of cost-effectiveness analysis capture all the estimated lifelong downstream benefits of treatment, including not only health gains but the potential for reducing or eliminating the costs of chronic treatment over many years. Thus, potential cures for expensive chronic conditions can be valued at extremely high one-time prices based largely on these cost offsets. SCD is not as expensive to care for as some other conditions, notably hemophilia, but consideration over whether full valuation of cost offsets as a part of the gene therapy price are still relevant.

There is nothing wrong with acknowledging the potential for cost offsets in the health system and beyond that may come with transformative therapy. However, assigning all that value in the pricing of treatments raises two fundamental questions. First, should the potential cure for an "expensive" condition be valued exponentially more than a potential cure for a condition that is less expensive, perhaps because it is rapidly fatal and does not accrue high costs over many years? And second, should the pricing of the therapy allocate to manufacturers "all" of the societal value at the incremental cost-effectiveness threshold, particularly when these kinds of treatments are far less likely to ever face generic competition that drives lower pricing?

We believe these two questions make it reasonable for manufacturers, payers, and other policymakers to consider alternatives to full valuation of potential cures based on 100% of cost offsets being assigned to the price of the treatment. There is no normative policy regarding whether a 50%-50% sharing of cost offsets or some other level is most appropriate. Further policy development is needed in this area, but as single-time potentially curative treatments start to come to market, all stakeholders should be aware that different cost-effectiveness scenarios should be considered in arriving at judgments about the ultimate "fair" price for these therapies.

Recommendation 4

Manufacturers should work with payers to create meaningful alternative payment models that can address two key distinguishing features of gene therapies: 1) the significant short-term budget impact; and 2) the considerable uncertainty regarding longer-term safety and benefits.

Attempts to design and implement alternative payment models for expensive one-time treatments are in their infancy in the US and other countries. The significant short-term budget impact of gene therapies can lead small employers to consider excluding all gene therapies from coverage, while larger health systems such as state Medicaid systems may have relatively inflexible budgets that cannot easily manage a surge of high-cost treatments. In addition, valuation of gene therapies must rely on some estimation of their long-term effects, yet substantial uncertainty remains about these effects at the time gene therapies are launched and first priced in the market. Manufacturers should work with payers and other stakeholders to make progress on designing and implementing novel payment mechanisms to address these issues. Alternative payment mechanisms include: 1) expanded use of stop-loss and other reinsurance programs; 2) installment payments linked to tracking of outcomes; 3) warranties linked to tracking of outcomes; 4) subscription payment models paying a set fee for entire populations; and 5) governmental risk pools or formal carve-outs to reduce the actuarial risk for smaller payers.

Clinicians and Clinical Societies

Recommendation 1

Prepare now to update treatment guidelines for patients with SCD immediately upon approval of gene therapies or other new transformative therapies in a form that is easy to interpret and use by clinicians, patients, and payers.

Payers frame their coverage policies using reviews of existing evidence and an understanding of best practice gained from authoritative clinical guidelines. Clinical societies should therefore be poised now to update their practice guidelines for managing patients with SCD the day that any therapies are approved by the FDA.

Patient Organizations

Recommendation 1

Patient organizations have a vital role to play in promoting objective descriptions of the risks and benefits of new therapies to support shared decision-making for every patient. In addition, patient groups have a powerful voice and should apply it to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system.

Advocacy and support groups helping people living with SCD should endeavor to educate patients about the potential risks and benefits of new therapies, particularly those with the potential for substantial harms, and work with other stakeholders to develop and disseminate evidence-based, balanced materials that are accessible to all patients, including those with low health literacy. Patient organizations should work with payers and clinical societies to improve access and to help hold manufacturers accountable for fair pricing.

Researchers/Regulators

Recommendation 1

The FDA, life science companies, and clinical researchers should adopt consistent measures of patient-important outcomes for SCD, including uniform definitions of VOC/VOEs.

Outcomes captured in clinical trials and through registries should reflect all aspects of living with sickle cell disease. Mental health outcomes were highlighted in the policy round table as often overlooked. Regarding VOC/VOEs, it is imperative that the FDA require manufacturer's to utilize uniform definitions in their trials and when possible, the FDA should seek to align eligibility criteria across trials – failure to do so fails the broader scientific and patient communities.

Recommendation 2

Manufacturers and the clinical research community should develop cohort studies and real-world evidence programs to evaluate the longer-term safety and durability of gene therapies.

The small sample sizes of the current trials leave substantial uncertainty about the potential for serious, but rare, longer-term harms such as myelodysplastic events. Additional data are needed to ascertain how lovo-cel, exa-cel and their related conditioning regimens will perform over time and in the real world.

Recommendation 3

Additional clinical trials are needed to compare the safety and efficacy of gene therapies to current standard of care (hematopoietic stem cell therapy [HSCT]).

In the absence of clinical trial data, clinicians, patients, and medical decision-makers (e.g., parents or guardians), and payers are likely to continue to consider HSCT with a sibling-matched donor as the gold standard for eligible patients. However, there is reason to believe that gene therapies may be less risky than traditional HSCT given that it does not impose a risk of graft versus host disease or rejection. Despite these risks, advances in HSCT have lowered the risk of this procedure over time and evidence would be likely be needed for gene therapy to supplant HSCT as standard of care.

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Supplemental Materials

A. Background: Supplemental Information

Some of these definitions are adapted from the 2020 ICER SCD review.

A1. Definitions

Acute chest syndrome[86]: Defined as a new radiodensity on chest radiography accompanied by fever and/or respiratory symptoms. Acute chest syndrome in adults with SCD requires prompt management to prevent clinical deterioration.

Acute kidney injury/renal infarction[87]: A condition resulting from a sudden disruption of blood flow to the renal artery. This may cause irreversible damage to kidney tissues.

Acute splenic sequestration[88]: Pooling of sickled red blood cells trapped in the spleen. This can cause the spleen to become enlarged, damaged, and not function properly. Splenic sequestration occurs more commonly in children and may cause sudden and severe anemia.

BCL11A[49]: A transcription factor that suppresses fetal hemoglobin. Disruption of this transcription factor results in increased expression of fetal hemoglobin.

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

Clustered regularly interspaces short palindromic repeats (CRISPR)-Cas9[89]: Bacterial immune system that enables insertion or deletion at certain genomic DNA sites.

Engraftment[90]: An indicator of a successful stem cell transplantation where an individual's body accepts transplanted bone marrow/stem cells and new blood cells begin to produce.

EuroQoL Visual Analog Scale (EQ VAS)[45]: A portion of the EQ-5D-5L scale that utilizes a vertical visual analog scale to allow an individual to self-report their current health state on a scale from 0 to 100, with 0 representing the worst imaginable health state and 100 being the best imaginable health state.

Functional Assessment of Cancer Therapy - General (FACT-G)[47,48]: A 27-item health-related quality of life instrument developed for patients receiving cancer treatment. The four domains of focus are physical, emotional, social, and functional-wellbeing with each item rated on a 5-point Likert-type scale for a total potential score of 108.

Bone Marrow Transplantation Subscale[46]: 12-item subscale of the FACT-G that assesses specific quality of life concerns related to bone marrow transplantation. It utilizes a Likert-type scale with scores ranging from 0 (not at all) to 4 (very much) for individual items.

Fetal hemoglobin[91]: A type of hemoglobin that is produced by a fetus's body during gestation and is replaced by adult hemoglobin during the first year of life. Fetal hemoglobin has a higher oxygen affinity than adult hemoglobin.

HbA^{T87Q}[43]: Modified adult hemoglobin designed to inhibit the polymerization of sickle hemoglobin.

HbSβ^0 thalassemia[92]: Occurs in patients who inherit one sickle cell gene and one beta thalassemia gene that results in no production of HbA.

HbSβ$^+$ thalassemia[92]: Occurs in patients who inherit one sickle cell gene and one beta thalassemia gene resulting in reduced production of HbA.

HbSC[92]: One inherited sickle cell gene ("S") and one abnormal Hb gene ("C"), which typically presents as milder anemia.

HbSD, HbSE and HbSO[92]: One inherited sickle cell gene ("S") and one gene from an abnormal type of Hb ("D,""E," or "O").

HbSS[92]: Two inherited sickle cell genes ("S") resulting in sickle cell anemia, the most common and severe form of SCD.

Hemolysis[93]: The breakdown of red blood cells. Common markers of hemolysis are reticulocyte count (elevated in hemolysis), levels of haptoglobin (decreased), lactate dehydrogenase (elevated during hemolysis, and total bilirubin (elevated).

Health Improvement Distribution Index (HIDI): The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4% = 2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above 1 suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. This statistic may be helpful in characterizing a treatment's contextual considerations and potential other benefits (Section 5). For the calculation for the HIDI

for Black Americans, we need the prevalence of Black Americans living with SCD and would divide that by the prevalence of all Americans living with SCD. Given that the vast majority of Americans living with SCD are Black Americans, we have approximated the HIDI for Black Americans by assuming that all of the 100,000 Americans living with SCD contribute to the prevalence of Black Americans living with SCD as well as the prevalence of all Americans living with SCD. Therefore, given that 13.6% of Americans are Black (or 13.6% * 334 Million = 45,424,000), the HIDI for Black Americans approaches 7.35.[2,94]

• Black Americans = (approaches 100,000 / 45,424,000) / (100,000 / 334,000,000) = approaches 7.35

Patient-Reported Outcome Measurement System® – Profile 57[95]: A self-reported questionnaire for adults ≥18 years old measuring physical, mental, and social health with seven domains and one pain intensity question. Domains include physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, and pain intensity.

Pulmonary arterial hypertension[96]: An elevation of pulmonary arterial systolic pressure (greater than 20 mmHg at rest or greater than 30 mmHg with exercise) determined by right heart catheterization.

Vaso-occlusive crisis (VOC): Pain as a result of decreased blood flow in the microcapillaries (can include blood vessel blockage) resulting in tissue ischemia, occurring most commonly in bone or bone marrow. VOCs are also known as vaso-occlusive episodes or acute pain crises. Definitions between pivotal trials vary and are listed in Table 3.3.

Table A1. Group Definitions of HGB-206 Trial Participants[38]

	Group A	Group B	Group C
Pre-Collection Transfusion Time	≤7 days	≥60 days	≥60 days
Method of HSPC Collection	Bone marrow harvest	Bone marrow harvest	Plerixafor and apheresis
AUC Target for Conditioning, uM* Min Per Dose	4000-4500 (medium)	5000 (high)	5000 (high)
Target Number of CD34+ Cells	≥1.5x10^6 per kg (low)	≥2x10^6 per kg (medium)	≥3x10^6 per kg (high)
Manufacturing Process	Original	Patient 1: Original/refined Patient 2: Refined	Refined

AUC: area under the curve, HSPC: hematopoietic stem and progenitor cell, kg: kilogram

A2. Potential Cost-Saving Measures in SCD

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 headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for SCD (e.g., reduction in disability), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of SCD beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with SCD that could be reduced, eliminated, or made more efficient.

It was suggested that sub-optimal care is often wasteful or lower-value and unfortunately, sub-optimal care is frequently encountered. If there were therapies that led to clinical cure and these therapies were delivered equitably, this would in theory reduce use of lower value care. However, if sub-optimal care were reduced or eliminated, this would benefit patients and potentially reduce the value of curative therapies such as exa-cel and lovo-cel.

In December of 2014, the American Society of Hematology put out a Choosing Wisely® recommendation against unnecessary routine red blood cells transfusions in SCD patients with chronic anemia or an uncomplicated pain crisis.[97] This recommendation was based on the potential increased risks of alloimmunization to minor blood group antigens and iron overload from repeated transfusions, as well as the lack of evidence in reduction in pain during an uncomplicated crisis.

B. Patient Perspectives: Supplemental Information

B1. Methods

During ICER's scoping phase and public comment periods, we received public comment submissions from two manufacturers and participated in conversations with nine key informants (four clinicians, one patient advocacy group, one person living with SCD, one caregiver, and two manufacturers). Organized by Sick Cells, we also conducted two focus groups with a total of 10 participants who were either people living with SCD or current or former caregivers. The feedback received from written input and scoping conversations helped us to understand and discuss the impact of SCD on patients and caregivers described in Section 2 of the report.

C. Clinical Guidelines

Some of the guideline descriptions are adapted from the 2020 report.

American Society of Hematology

2021 Guidelines for SCD: Stem Cell Transplantation[98]

A multidisciplinary guideline panel formed by the American Society of Hematology agreed on eight recommendations to guide patients with SCD and their providers in the consideration of HSCT. All recommendations outlined below are classified by the panel as conditional recommendations (described as suggestions) meaning there is "very low certainty in the evidence about effects."

For patients who have experienced overt stroke or an abnormal transcranial Doppler ultrasound, the panel suggests HLA-matched related HSCT over standard of care, which may include hydroxyurea or transfusion. For patients with an indication for HSCT but lack a matched-sibling donor, the panel suggests transplants for alternative donors. Patients who are eligible for HSCT are suggested to use allogeneic transplantation at earlier ages rather than older.

For patients with frequent pain or recurrent episodes of acute chest syndrome, the panel suggests matched allogenic transplantations over standard of care. For allogenic HSCT, using chemotherapy-based conditioning regimens or total body irradiation ≤400 cGy is suggested.

For children with an indication for allogeneic HSCT and matched-sibling donor, the panel suggests myeloablative condition rather than reduced-intensity conditioning. Alternatively, for adults with the same indication and matched-sibling donor, nonmyeloablative conditioning is suggested over reduced-intensity conditioning.

Lastly, the guideline suggests the use of HLA-identical sibling cord blood when available over bone barrow.

2020 Guidelines for SCD: Management of Acute and Chronic Pain[99]

A multidisciplinary guideline panel formed by the American Society of Hematology agreed on 18 recommendations to guide patients and providers in pain management decisions. These range from strong recommendations based on low certainty to conditional recommendations based on low certainty in evidence about the effects, with the majority being conditional.

For children and adults with SCD with acute pain related to SCD in an acute care setting, the panel recommends both a rapid assessment and analgesic administration to manage pain levels. If opioid therapy is indicated for a patient in this scenario, tailored-opioid dosing is suggested. In addition, a

short course of non-steroidal anti-inflammatory drugs (NSAIDs) is suggested. The guideline panel suggests against the use of corticosteroids for acute pain. If an adult or child is hospitalized due to acute pain, the panel suggests an analgesic ketamine infusion if pain is not resolved from opioid treatment. Regional anesthesia is suggested for localized pain if opioid treatment does not effectively reduce pain. SCD-specific hospital acute care facilities are suggested over traditional emergency room care for people requiring hospital care for acute pain episodes.

For adults with SCD with chronic pain from avascular necrosis of the bone, duloxetine, and NSAIDS as management treatments are suggested. For adults with chronic pain but no cause beyond SCD complications, the use of serotonin and norepinephrine reupdate inhibitors, tricyclic antidepressants, and gabapentinoids as options for treatment are suggested.

For adults and children with SCD-related chronic pain, cognitive and behavioral treatment plans are suggested. Additionally, alternative approaches (e.g., acupuncture) are suggested for adults.

If a person's chronic pain is recent, the initiation of chronic opioid therapy is not suggested unless they are refractory to other treatment methods. If chronic opioid therapy is initiated for a person with chronic pain and is showing a benefit, shared decision making to assess the continuation of chronic opioid therapy is suggested. However, if benefit is not shown from chronic opioid therapy, discontinuation is suggested.

Lastly, monthly transfusion therapy is not suggested as a first-line treatment for adults and children with SCD and recurrent acute pain. The panel does not provide a suggestion for the use of monthly transfusion therapy for the treatment of chronic pain from SCD.

2020 Guidelines for SCD: Transfusion Support[100]

A multidisciplinary guideline panel formed by the American Society of Hematology agreed on 10 recommendations for the screening, prevention, and management of iron overload, alloimmunization, and delayed hemolytic transfusion reactions.

Before the first transfusion or at the earliest opportunity, the panel suggests obtaining an extended red cell antigen profile by genotype or serology for all SCD patients and recommends prophylactic red cell antigen matching for Rh and K antigens for those receiving transfusions. The panel suggests immunosuppressive therapy in SCD patients with an acute need for transfusion and who are at increased risk of acute hemolytic transfusion reactions or with a history of multiple or delayed hemolytic transfusion reactions and ongoing hyperhemolysis.

For SCD patients receiving chronic transfusions, the panel suggests using automated red cell exchange transfusions rather than simple or manual red cell exchange; either conventional red cell exchange or red cell exchange with isovolemic hemodilution is recommended for this population.

In addition, the panel suggests iron overload screening for liver iron content by magnetic resonance imaging every one to two years.

For patients with severe acute chest syndrome, the panel suggests automated transfusion over manual red cell exchange and in those with moderate acute chest syndrome, the panel suggests automated red cell exchange, manual red cell exchange or simple transfusion methods.

For pregnant patients with SCD, the panel suggests either standard care or prophylactic transfusion at regular intervals. More broadly, for patients with SCD undergoing surgery requiring general anesthesia or lasting more than an hour, preoperative transfusion is suggested.

2019 Guidelines for SCD: Cardiopulmonary and Kidney Disease[96]

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

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

National Heart, Lung, and Blood Institute

Evidence-Based Management of SCD: Expert Panel, 2014[101]

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

Health Maintenance (With Focus on Outcomes Listed Above)

- Only in children with sickle cell anemia (does not include those with HbSC, HbSD, HbSβ0 thalassemia, or HbSβ+ thalassemia), from age two through at least 16, the panel strongly recommends annual screening with transcranial doppler (imaging for the risk of stroke).

Management of Acute Complications of SCD (With Focus on Outcomes Listed Above)

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

Hydroxyurea Therapy for Management of SCD (With Focus on Outcomes Listed Above)

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

Blood Transfusions for Management of SCD (With Focus on Outcomes Listed Above)

- Prior to undergoing a surgical procedure, the guidelines state that all adults and children with sickle cell anemia are to be transfused with red blood cells to raise hemoglobin level to 10 g/dL.
- For both children and adults, the guidelines suggest consulting a blood bank for a workup of possible delayed hemolytic transfusion reaction, for patients showing signs of acute anemia, jaundice, or pain within three weeks after a blood transfusion.
- For patients receiving chronic transfusion therapy, the guidelines recommend performing serial assessment of iron overload.

- In children with transcranial doppler results >170 cm/sec, the guidelines recommend referral to a specialist who may initiate chronic transfusion therapy for the prevention of stroke.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

Population, Interventions, Comparators, Outcomes, Timing, Settings

Population

The population of focus for this review is adolescents and adults with severe SCD and 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., hemoglobin SS, SC, SD).

Interventions

The full list of interventions is as follows:

- lovo-cel (bluebird bio)
- 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., VOC)
    - 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 hemoglobin, fetal hemoglobin, HbAT87Q, HbS)
        - Hemolysis markers (e.g., reticulocyte count, indirect bilirubin levels, haptoglobin, lactate dehydrogenase)
    - Caregiver burden
    - 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.

Study Design

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.

Table D1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.

Section and Topic	Item #	Checklist Item
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.

Section and Topic	Item #	Checklist Item
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on gene therapies for sickle cell disease followed established best research methods.[102,103] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[104] The PRISMA guidelines include a checklist of 27 items.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE) as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/. Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer.org/guidelines-on-icers-acceptance-and-use-of-in-confidence-data-from-manufacturers-of-pharmaceuticals-devices-and-other-health-interventions/).

Table D2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

1	exp anemia, sickle cell/
2	((sickle adj3 (disease or an?emia)) or “sickle cell” or meniscocyt* or drepanocyte* or sickl* or (SC adj3 (disease or an?emia))).ti,ab.
3	hemoglobin, sickle/ or (h?emoglobin adj5 sickl*).ti,ab.
4	((h?emoglobin or hb or hb- or hgb) adj3 (SS or S-S or SC or S-C or SB* or b0 or S-beta or thalassemia or beta-zero or beta plus)).ti,ab.
5	1 or 2 or 3 or 4
6	(lovo-cel or “lovo cel” or lovocel or “lovotibeglogene autotemcel” or bb1111 or “bb 1111” or bb-1111 or LentiGlobin or “LentiGlobin SCD” or BB305).ti,ab.
7	(exa-cel or “exa cel” OR exacel OR CTX001 OR “CTX 001” OR CTX-001).ti,ab.
8	6 or 7
9	5 and 8
10	("address" or "autobiography" or "bibliography" or "biography" or "case reports" or "comment" or "congress" or "consensus development conference" or "duplicate publication" or "editorial" or "guideline" or "interview" or "lecture" or "legal case" or "legislation" or "letter" or "news" or "newspaper article" or "patient education handout" or "periodical index" or "personal narrative" or "portrait" or "practice guideline" or "review" or "video-audio media").pt.
11	9 not 10
12	(animals not (humans and animals)).sh.
13	11 not 12
14	Limit 13 to English language
15	Remove duplicates from 14

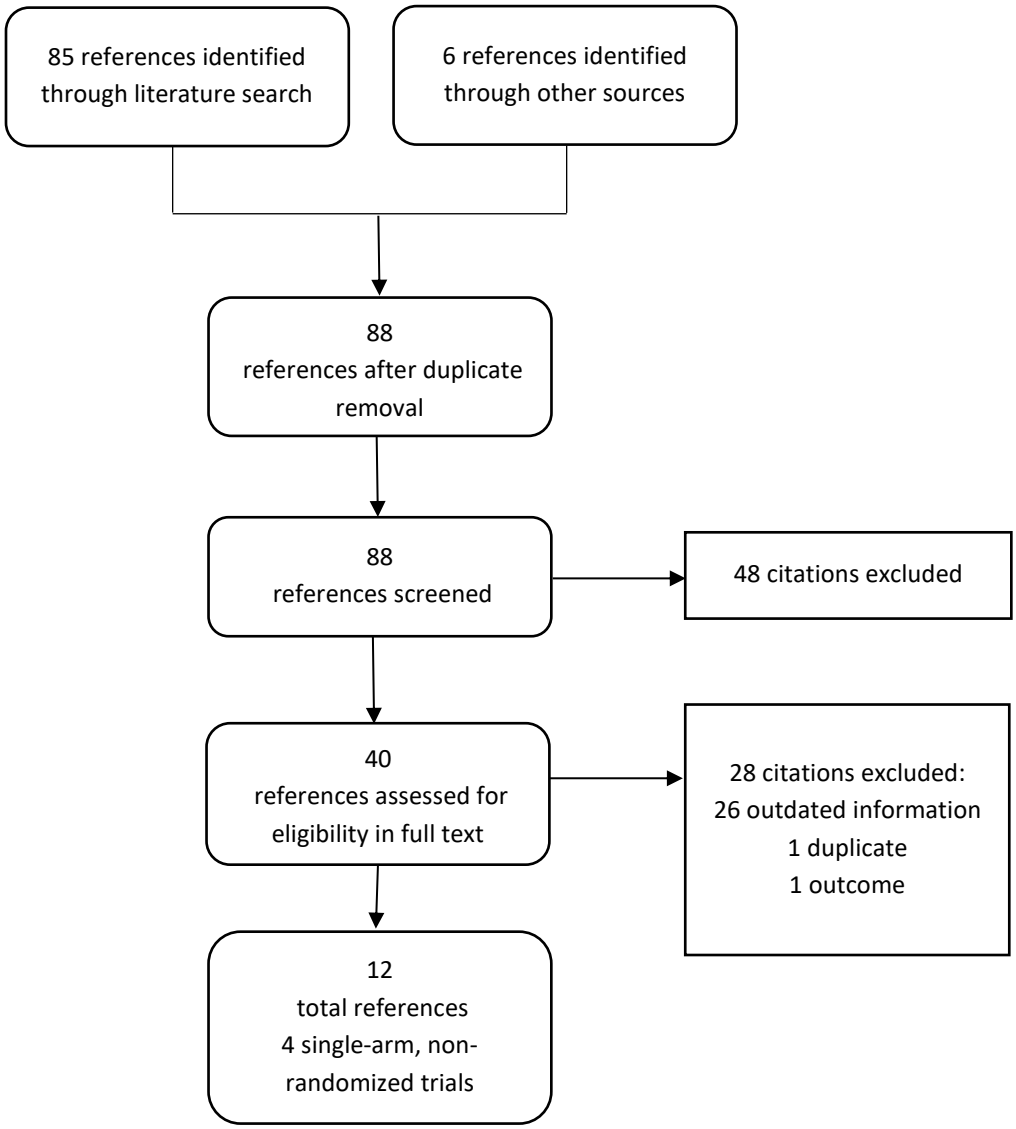
Search last updated on May 30, 2023.

Table D3. Search Strategy of EMBASE SEARCH

#1	'sickle cell anemia'/exp
#2	((sickle NEAR/3 (disease OR an*emia)):ti,ab) OR 'sickle cell':ti,ab OR meniscocyt*:ti,ab OR drepanocyte*:ti,ab OR sickl*:ti,ab OR ((sc NEAR/3 (disease OR an*emia)):ti,ab)
#3	'hemoglobin s'/exp OR ((h?emoglobin NEAR/5 sickl*):ti,ab)
#4	((h?emoglobin OR hb OR 'hb-' OR hgb) NEAR/3 (ss OR 's-s' OR sc OR 's-c' OR 'sb' OR b0 OR 's-beta' OR thalassemia OR 'beta-zero' OR 'beta plus')):ti,ab
#5	#1 OR #2 OR #3 OR #4
#6	'lovotibeglogene autotemcel'/exp
#7	('lovo-cel' OR 'lovo cel' OR lovocel OR bb1111 OR 'bb 1111' OR 'bb-1111' OR LentiGlobin OR 'LentiGlobin SCD' OR BB305):ti,ab
#8	#6 OR #7
#9	'exagamglogene autotemcel'/exp
#10	('exa-cel' OR 'exa cel' OR exacel OR CTX001 OR 'CTX 001' OR 'CTX-001'):ti,ab
#11	#9 OR #10
#12	#8 OR #11
#13	#5 AND #12
#14	('addresses' OR 'autobiography' OR 'bibliography' OR 'biography' OR 'case report' OR 'comment' OR 'congresses' OR 'consensus development conference' OR 'duplicate publication' OR 'editorial' OR 'guideline' OR 'in vitro' OR 'interview' OR 'lecture' OR 'legal cases' OR 'legislation' OR 'letter' OR 'news' OR 'newspaper article' OR 'patient education handout' OR 'periodical index' OR 'personal narratives' OR 'portraits' OR 'practice guideline' OR 'review' OR 'video audio media')/it
#15	#13 NOT #14
#16	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#17	#15 NOT #16
#18	#17 AND [English]/lim

Search last updated on May 30, 2023.

Figure D1. PRISMA Flowchart Showing Results of Literature Search for Gene Therapies for SCD



Study Selection

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

Data Extraction and Quality Assessment

Data were extracted into Excel. The basic design and elements of the extraction forms followed those used for other reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, and results. The data extraction was performed in the following steps:

1) One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.

2) Extracted data was reviewed for logic, and a random proportion of data was validated by a third investigator for additional quality assurance.

Because studies in our evidence base were non-randomized and lacked a placebo or active control group, we did not assign any quality ratings to these trials. The limitations, uncertainties, and gaps in evidence of these trials are discussed in the Uncertainty and Controversies section.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Supplement D).[105,106]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for these newer treatments, we performed an assessment of publication bias on for lovo-cel and exa-cel using ClinicalTrials.gov. Search terms included "lovotibeglogene autotemcel," "lovo-cel," "exagamglogene autotemcel," and "exa-cel." We scanned the site to identify studies which would have met our inclusion criteria and for which no findings have been published and did not find any evidence of publication bias.

Data Synthesis and Statistical Analyses

Data on key outcomes of the main studies were summarized in evidence tables (see Section D2 below) and synthesized qualitatively and quantitatively in the body of the report. Key differences between studies (study design, patient characteristics, interventions, outcomes, study quality) were explored in the text of the report. We assessed the feasibility of quantitative synthesis and due to differences in the trials, we did not conduct a meta-analysis or network meta-analysis to compare lovo-cel to exa-cel.

D2. Evidence Tables

Table D4. Study Design

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
HGB-206 Kanter 2022 & Walters 2022[38,39,63] NCT02140554	Phase I/II, single-arm, open-label, nonrandomized trial Follow-up: 24 months post-transplant	Modified Group C: Patients with severe SCD with ≥4 severe VOCs in 2 years before screening N=36	LentiGlobin BB305 (lovo-cel) administered by IV infusion following myeloablative conditioning with busulfan	**Inclusion (Group C):** -Be ≥12 and ≤50 of age -Have severe SCD (≥4 severe VOEs in the 24 months prior to informed consent), with either βS/βS or βS/β0 or βS/β+ genotype -Karnofsky performance status of ≥ 60 (age ≥16 years) or a Lansky performance status of ≥60 (age <16 years) -Hydroxyurea failure or intolerance -Treated/followed for ≥24 months prior to consent in medical center(s) with records on SCD history **Exclusion:** -Applicable to subjects <18 years of age only: availability of a willing, matched HLA-identical sibling hematopoietic cell donor -HIV-1, HIV-2, HBV, HCV -Infection, advanced liver disease, inadequate bone marrow function, malignancy or immunodeficiency disorder -History of severe cerebral vasculopathy -Contraindications to plerixafor, busulfan and any other conditioning medicinal products -Prior receipt of allogeneic transplant or gene therapy -Immediate family with familial cancer syndrome -Pregnancy or breastfeeding in a postpartum female or absence of adequate contraception -Need therapeutic anticoagulation therapy during	Proportion of participants achieving complete resolution of severe VOEs (6-18 mo. post-transplant)

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
				conditioning -Unable to receive RBC transfusion	
HGB-205 Magrin 2022[60] NCT02151526	Phase I/II, single-arm, open-label, nonrandomized trial Follow-up: 24 months post-transplant	Subgroup of interest: Patients with SCD with recurrent VOCs N=3	LentiGlobin BB305 (lovo-cel) administered by IV infusion following myeloablative conditioning with busulfan	**Inclusion (Overall population):** -Ages 5-35 years with severe SCD or transfusion dependent beta-thalassemia major -Eligible for allogeneic HSCT without a matched related donor -Treated/followed for ≥2 years in a specialized center with maintained detailed medical records -Participants with severe SCD also must: fail hydroxyurea treatment for ≥4 months and must have ≥1 poor prognostic risk factor: 1) recurrent VOCs (≥2 episodes in preceding year) 2) significant cerebral abnormality on MRI 3) stroke without severe cognitive disability 4) osteonecrosis of ≥2 joints 5) anti-erythrocyte alloimmunization 6) sickle cell cardiomyopathy 7) ACS (≥2 episodes) **Exclusion:** -Availability of 10/10 matched HLA identical sibling hematopoietic cell donor -Infection, malignancy, myeloproliferative, or immunodeficiency disorder -WBC count <3×10^9/L and/or platelet count <120×10^9/L -History of major organ damage	-Participants with successful neutrophil and platelet engraftment [through mo. 24] -Time to neutrophil and platelet engraftment [through mo. 24] -Transplant related mortality [through 1-year post-transplant] -Participants with OS events [from infusion through mo. 24] -Participants with vector-derived RCL [from infusion through mo. 24] -Participants with >% contribution of an individual clone as per ISA [through mo. 24] -AEs and SAEs [up to mo. 24]

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
CLIMB-121 Frangoul 2022[40,107] NCT03745287	Phase I/II/III, single-arm, open-label, nonrandomized trial Follow-up: 24 months post-transplant	Patients with severe SCD and a history of ≥2 VOCs per year in 2 years before screening N=35	CTX001 by IV infusion following myeloablative conditioning with busulfan	**Inclusion:** -Ages 12-35 years with a diagnosis of severe SCD defined by: 1) documented severe SCD genotype and 2) history of at least 2 severe VOCs per year for 2 years prior to enrollment -Eligible for ASCT **Exclusion:** -An available 10/10 HLA-matched related donor -Prior HSCT -Significant or active infection	-Proportion of participants free of severe VOCs for at least 12 mo. [up to 2 years after infusion] -Proportion of participants with neutrophil engraftment [within 42 days after infusion] -Time to engraftment [up to 2 years after infusion] -Frequency and severity of AEs [up to 2 years after infusion] -Incidence of TRM [within 100 days after infusion] -Incidence of TRM within 1 year after CTX001 infusion [up to 1 year after infusion] -All-cause mortality [2 years after mobilization]

ACS: acute chest syndrome, AE: adverse event, ER: emergency room, HBV: hepatitis B virus, HCV: hepatitis C virus, HIV: human immunodeficiency virus, HLA: human leukocyte antigen, HSCT: hematopoietic stem cell transplantation, IV: intravenous, L: liter, N: total number, NCT: National Clinical Trial, NR: not reported, NSAID: nonsteroidal anti-inflammatory drug, RBC: red blood cell, SAE: serious adverse event, SCD: sickle cell disease, TPVOE: transplant population with vaso-occlusive events, VOC: vaso-occlusive crisis, VOE: vaso-occlusive event, WBC: white blood cell

Table D5. Baseline Characteristics: lovo-cel[38,39,63]

HGB-206			
Characteristic		**N**	**lovo-cel: Group C**
Age, Median Years (Range)		35	24 (12-38)
Age Distribution, n (%)	**12-17 Years**	35	8 (23)
	18-50 Years	35	27 (77)
Female Sex, n (%)		35	13 (37)
Race (Black), n (%)		35	34 (97)
βS/βS Genotype, n (%)		35	35 (100)
βS/β0 Genotype, n (%)		35	0 (0)
Annualized Incidence of Severe VOEs* in 24 Months Before Enrollment, Median (Range)		32	3 (0.5-13.5)
Hydroxyurea Use ≤3 Months Before Enrollment, n (%)		35	23 (66)
History of Stroke, n (%)		35	5 (14)
History of Tricuspid Regurgitant Jet Velocity of ≥2.5 m Per Second, n (%)		35	6 (17)
Total Hb Level, Median g/dL		22	8.5

dL: deciliter, g: gram, Hb: hemoglobin, m: meter, n: number, N: total number, VOE: vaso-occlusive event

*Severe VOE was defined in the protocol as an event, with no medically determined cause other than a vaso-occlusion, requiring a ≥24-hour hospital or ER observation unit visit or at least 2 visits to a day unit or ER over 72 hours with both visits requiring IV treatment. Refer to Table A1 for a more detailed definition.

Table D6. Baseline Characteristics: exa-cel[40,44,107]

CLIMB-121		
Characteristic		**Exa-cel**
N		**35**
Age, mean years (range)		22.1 (12-34)
Age distribution, n (%)	**12-17 years**	8 (22.9)
	18-34 years	27 (77.1)
Female sex, n (%)		16 (45.7)
βS/βS Genotype, n (%)		33 (94.3)
βS/β0 genotype, n (%)		2 (5.7)
Severe VOC* incidence per year during the 2-year period before screening, mean (range)		4.2 (2-18.5)
In-patient hospitalizations for severe VOCs per year during the 2-year period before screening, mean units (range)		2.6 (0.5-8.5)
total Hb level, mean g/dL		9.1†

dL: deciliter, g: gram, Hb: hemoglobin, n: number, N: total number, VOC: vaso-occlusive crisis

*Severe VOC was defined in the protocol as the occurrence of at least two of the following events each year during the two-year period before screening: acute pain event that requires a visit to a medical facility and administration of pain medications or RBC transfusions, ACS, priapism lasting >2 hours and requiring a visit to a medical facility, or splenic sequestration. Refer to Table A1 for a more detailed definition.

†Data are from an earlier cut-off date of February 2022 (N=30).

Table D7. Efficacy Outcomes: lovo-cel[38,39,63]

HGB-206			
Outcome	**Timepoint**	**N**	**lovo-Cel: Group C**
Group C TPVOE Subgroup			
Proportion of Participants Achieving Complete Resolution of VOEs*, n (%)	6-18 months post-transplant	10†	9 (90)
VOE*, Median Rate Per Year (Range)	6-18 months post-transplant	10†	0 (0-5.9)
Proportion of Participants Achieving Complete Resolution of Severe VOEs*, n (%)	6-18 months post-transplant	31	30 (96.8)
Severe VOE*, Median Rate Per Year (Range)	6-18 months post-transplant	31	0 (0-0.5)
Group C Overall			
Total Hb Level, Median g/dL	Baseline	22	8.5
	3 months	35	11.4
	6 months	32	11.5
	9 months	32	11.5
	12 months	31	12
	15 months	23	12
	18 months	22	12.1
	21 months	14	11.9
	24 months	16	11.7
Vector Copy Number in Peripheral Blood, Median c/dg	12 months	24	1.2
	36 months	4	2.3
HbAT87Q Fraction in Non-Transfused Total Hb, Median %	Baseline	22	NA
	3 months	35	46
	6 months	32	47
	9 months	32	45
	12 months	31	45
	15 months	23	46
	18 months	22	44
	21 months	14	44
	24 months	16	45
Successful Neutrophil/Platelet Engraftment, n (%)	After infusion	35	100 (100)
Time to Neutrophil Engraftment, Median (Range) Days	After infusion	35	20 (12-35)

HGB-206			
Outcome	**Timepoint**	**N**	**lovo-Cel: Group C**
Time to Platelet Engraftment, Median (Range) Days	After infusion	35	36 (18-136)
Days of Hospitalization from Conditioning to Discharge, Mean (Range) Days	After infusion	35	35 (26-65)

c: copies, dg: diploid genome, dL: deciliter, g: gram, Hb, hemoglobin, n: number, N: total number, NA: not applicable, TPVOE: transplant population with vaso-occlusive events, VOC: vaso-occlusive event

*Severe VOE was defined in the protocol as an event, with no medically determined cause other than a vaso-occlusion, requiring a ≥24-hour hospital or ER observation unit visit or at least two visits to a day unit or ER over 72 hours with both visits requiring intravenous treatment. Refer to Table A1 for a more detailed definition.

†Based off the number of participants with at least 18 months of follow-up; data cut-off February 2021.

Table D8. Efficacy Outcomes: exa-cel[40,44,107]

CLIMB-121			
Outcome	**Timepoint**	**N**	**Exa-cel**
Proportion of participants who have not experienced severe VOCs for at least 12 consecutive months, n (%)	From 60 days after last RBC transfusion up to 2 years after exa-cel infusion	17	16 (94.1) 95% CI: (71.3%-99.9%)
Proportion of participants free from in-patient hospitalizations for severe VOCs for ≥12 consecutive months, n (%)	From 60 days after last RBC transfusion up to 2 years after exa-cel infusion	17	17 (100) 95% CI: (80.5%-100%)
Time to last RBC transfusion, mean days (range)	after infusion	17	22.5
Proportion of HbF against total Hb, mean %	Baseline	35	*4.8*†
	3 months	34	36.8
	6 months	29	*42.4*†
	9 months	29	*41.9*†
	12 months	17	*42.7*†
	15 months	16	*42.2*†
	18 months	12	*41.9*†
	21 months	6	*39.4*†
	24 months	4	*43.2*†
Total Hb level, mean g/dL	Baseline	30	9.1‡
	3 months	25	12.1‡
	6 months	17	12.7‡
	9 months	15	13.3‡
	12 months	9	12.5‡
	15 months	6	13.7‡
	18 months	3	12.1‡
	21 months	2	11.4‡
	24 months	1	11.3‡
	27 months	1	11.4‡
	30 months	1	10.6‡

CLIMB-121			
Outcome	**Timepoint**	**N**	**Exa-cel**
Successful neutrophil/platelet engraftment, n (%)	after infusion	35	35 (100)
Time to neutrophil engraftment, median (range) days	after infusion	35	27 (15-40)
Time to platelet engraftment, median (range) days	after infusion	35	33 (23-81)
Proportion of edited BCL11A alleles in bone marrow CD34+HSPCs, mean %	6 months	7	86.6%‡
Proportion of edited BCL11A alleles in peripheral blood mononuclear cells, mean %	6 months	17	76.0%‡

dL: deciliter, g: gram, Hb: hemoglobin, HbF: fetal hemoglobin, HSPC: hematopoietic stem and progenitor cell, n: number, N: total number, RBC: red blood cell, VOC: vaso-occlusive crisis

*Severe VOC was defined in the protocol as the occurrence of at least 2 of the following events each year during the 2-year period before screening: acute pain event that requires a visit to a medical facility and administration of pain medications or RBC transfusions, ACS, priapism lasting >2 hours and requiring a visit to a medical facility, or splenic sequestration. Refer to Table A1 for a more detailed definition.

†Data have been digitized.

‡Data are from an earlier cut-off date of February 2022.

Table D9. Patient-Reported Outcomes: Lovo-cel[42]

		HGB-206: Group C Overall							
		Patients with Baseline Score "Worse" than Population Norm				Patients with Baseline Score "Better or Near" than Population Norm			
		Timepoint: At Month 6 Up to Month 24							
		Baseline		Last Visit		Baseline		Last Visit	
		Score	n	Score	n	Score	n	Score	n
PROMIS-57	**Pain Intensity**	6.5	15	1.8	5	2	9	2.8	4
	Pain Interference	64.2	16	44.5	5	46.4	8	45.9	4
	Fatigue	64.6	8	46.9	1	47.7	16	43.4	9

n: number, PROMIS: Patient-Reported Outcomes Measurement Information System

Table D10. Patient-Reported Outcomes: Exa-cel [44]

CLIMB-121					
Timepoint		**n**	**EQ VAS**	**FACT-G Total Score**	**BMT Score**
Baseline, mean points (SD)		17	63.5 (22.5)	67.5 (18.3)	26.1 (3.5)
Change from baseline, mean points (SD)	**Month 6**	16	24.3 (27.1)	16.5 (17.4)	3.6 (6.2)
	Month 12	17	25.3 (23.2)	20.5 (18)	5.3 (4.5)
	Month 18	11	33.1 (17.2)	27.2 (20.3)	6.7 (4.2)

BMT: bone marrow transplantation subscale, EQ VAS: EuroQol visual analog scale, FACT-G: Functional Assessment of Cancer Therapy-General, n: number, SD: standard deviation

Table D11. Safety: Lovo-cel[38]

HGB-206			
Outcome		**N**	**lovo-Cel: Group C Overall**
AE, n (%)	**Due to Plerixafor Mobilization or Apheresis**	43*	22 (51)
	Due to Conditioning	35	35 (100)
	After lovo-cel Infusion	35	35 (100)
SAE, n (%)	**Due to Plerixafor Mobilization or Apheresis**	43*	5 (12)
	Due to Conditioning	35	5 (14)
	After lovo-cel Infusion	35	15 (43)
≥ Grade 3 AE, n (%)	**Due to Plerixafor Mobilization or Apheresis**	43*	11 (26)
	Due to Conditioning	35	32 (91)
	After lovo-cel Infusion	35	34 (97)
	Stomatitis	35	24 (69)
	Thrombocytopenia	35	23 (66)
	Neutropenia	35	19 (54)
	Febrile Neutropenia	35	15 (43)
	Anemia	35	13 (37)
	Leukopenia	35	11 (31)
Treatment-Related AE after Infusion, n (%)		35	3 (9)
Death, n (%)		35	1 (2.9)
Hematologic Malignancies, n (%)		35	0 (0)
Veno-Occlusive Liver Disease		35	0 (0)
Graft Failure		35	0 (0)
Vector-Mediated Insertional Oncogenesis		35	0 (0)
Replication-Competent Lentivirus Incidence, n (%)		35	0 (0)

AE: adverse event, n: number, N: total number, NR: not reported, SAE: serious adverse event

*Refers to number of patients who underwent stem cell collection. Not all 43 patients received lovo-cel infusion.

Table D12. Safety: exa-cel[40,44,107]

CLIMB-121		
Outcome		**Exa-cel**
N		**35**
AE, n (%)	**Any**	35 (100)
	Related to exa-cel	12 (34.3)
	Related to busulfan	35 (100)
	Grade 3/4	34 (97.1)
SAE, n (%)	**Any**	14 (40)
	Related to exa-cel	0
Death, n (%)		1 (2.9)*
Malignancies, n (%)		0
AEs in ≥50% of participants, n (%)	**Nausea**	26 (74.3)
	Stomatitis	24 (68.6)
	Vomiting	21 (60)
	Abdominal pain	20 (57.1)
	Constipation	19 (54.3)
	Decreased appetite	19 (54.3)
	Platelet count decreased	19 (54.3)
	Febrile neutropenia	18 (51.4)
	Headache	18 (51.4)
	Pain in extremity	18 (51.4)

AE: adverse event, n: number, N: total number, SAE: serious adverse event

*Death occurred after the February 2022 data cut-off. An adult participant developed pneumonia and respiratory failure, resulting in death. The investigator attributed this to SARS-CoV-2 infection, potentially related to busulfan lung injury, but unrelated to exa-cel.

D3. Ongoing Studies

Table D13. Ongoing Studies

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcome(s)	Estimated Completion Date
lovo-cel					
A Study Evaluating Gene Therapy With BB305 Lentiviral Vector in SCD (HGB-210) Bluebird bio NCT04293185	Phase III Single-arm, open-label, nonrandomized trial N~35	LentiGlobin BB305 (lovo-cel) administered by IV infusion following myeloablative conditioning with busulfan	**Inclusion Criteria:** -Diagnosed with SCD, with βS/βS, βS/β0, or βS/β+ genotype -≥2 and ≤50 years of age and weigh ≥6 kg -Karnofsky performance status of ≥60 (age ≥16 years) or Lansky performance status of ≥60 (age <16 years) -Treated and followed for ≥24 months in medical center with records on SCD history -Experienced ≥4 VOEs in 24 months -HU failure/intolerance **Exclusion Criteria:** -Appropriate allo-HSCT and available HLA-matched related hematopoietic stem cell donor -Severe cerebral vasculopathy -HIV-1, HIV-2, HTLV-1, HBV, HCV, active syphilis -Active infection, advanced liver disease, inadequate bone marrow function -Contraindication to plerixafor, busulfan, other conditioning products -Needing therapeutic anticoagulation treatment during conditioning -Unable to receive PRBC transfusion -Receipt of allogeneic transplant or gene therapy -Malignancy or immunodeficiency disorder -Family with familial cancer syndrome -Breastfeeding or pregnant -Ineligible for HSCT	**6-18 months post-transplant:** -Proportion of participants achieving complete resolution of VOEs (VOE-CR)	October 2026

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcome(s)	Estimated Completion Date
			-Abnormality or genetic mutation that may increase risk of MDS or AML -Genetic mutations resulting in inactivation of ≥2 α-globin genes		
Long-term Follow-up of Subjects With SCD Treated With Ex Vivo Gene Therapy Bluebird bio NCT04628585	Long-term follow-up observational study N~85	LentiGlobin BB305 (lovo-cel) administered by IV infusion following myeloablative conditioning with busulfan (followed 15 years post-drug infusion)	**Inclusion Criteria:** -Ages 2-53 years -Participants with SCD treated with ex vivo gene therapy product in bluebird bio-sponsored clinical studies (HGB-210, HGB-206, HGB-205)	**Up to 15 years post-infusion:** -Immune-related AEs -New/worsening hematologic disorders -New/worsening neurologic disorders -Malignancies	January 2038
exa-cel					
Evaluation of Safety and Efficacy of CTX001 in Pediatric Participants With Severe SCD (CLIMB-151) Vertex Pharmaceuticals Incorporated NCT05329649	Phase III Single-arm, open-label, nonrandomized trial N~12	CTX001 by IV infusion following myeloablative conditioning with busulfan	**Inclusion Criteria:** -Ages 2 to 11 years -Diagnosis of severe SCD as defined by history of ≥2 severe VOCs events per year for 2 years prior to enrollment -HU failure/intolerance -Eligible for ASCT **Exclusion Criteria:** -10/10 HLA-matched related donor -HSCT -Active infection	**Up to 24 months post-infusion:** -No severe VOCs for ≥12 months	May 2026
Evaluation of Efficacy and Safety of a Single Dose of CTX001 in Participants With Transfusion-Dependent β-Thalassemia and Severe SCD	Phase IIIb Single-arm, open-label, nonrandomized trial N~12	CTX001 by IV infusion following myeloablative conditioning with busulfan	**Inclusion Criteria:** -For participants with TDT and SCD (overall): Eligible for ASCT -For participants with TDT: 1) homozygous β-thalassemia or compound heterozygous β-thalassemia 2) history of ≥100 mL/kg/year or 10	**Up to 12 months post-infusion:** -HbF Concentration Over Time	February 2025

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcome(s)	Estimated Completion Date
Vertex Pharmaceuticals Incorporated NCT05477563			units/year of PRBC transfusions in 2 years before consent -For participants with SCD: severe SCD with 1) SCD genotypes, 2) ≥2 severe VOCs events/year for 2 years prior to enrollment **Exclusion Criteria:** -For Participants with TDT and SCD (overall): 1) HLA-matched related donor is available, 2) prior HSCT, 3) active infection -For participants with TDT: 1) Associated α-thalassemia and >1 alpha deletion, or alpha multiplications, 2) sickle cell β-thalassemia variant -For participants with SCD: Moyamoya syndrome	-Hb Concentration Over Time	
A Long-term Follow-up Study in Subjects Who Received CTX001 Vertex Pharmaceuticals Incorporated NCT04208529	Phase III Long-term follow-up observational study N~114	CTX001 by IV infusion following myeloablative conditioning with busulfan (followed 15 years post-drug infusion)	**Inclusion Criteria:** -Ages 2 years and older -Completed or discontinued the parent study (CTX001-111 or CTX001-121 or VX21-CTX001-141 or VX21-CTX001-151) after CTX001 infusion	**Up to 15 years post-infusion:** -New malignancies -New/worsening hematologic disorders -All-cause mortality -SAEs -CTX001-related AEs	September 2039

AE: adverse event, AML: acute myeloid leukemia, CR: complete resolution, Hb: hemoglobin, HbF: fetal hemoglobin, HBV: hepatitis B, HCV: hepatitis C, HIV: human immunodeficiency virus, HLA: human leucocyte antigen, HSCT: hematopoietic stem cell transplantation, HTLV: human T-lymphotropic virus, HU: hydroxyurea, IV: intravenous, kg: kilogram, N: number, MDS: myelodysplastic syndrome, PRBC: packed red blood cell, RBC: red blood cell, SAE: serious adverse event, SCD: sickle cell disease, TDT: transfusion-dependent thalassemia, VOC: vaso-occlusive crisis, VOE: vaso-occlusive event
Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

D4. Previous Systematic Reviews and Technology Assessments

We identified one ongoing health technology assessment conducted by the National Institute for Health and Care Excellence and one previously conducted review of curative therapies for SCD. Both are briefly summarized below.

National Institute for Health and Care Excellence Technology Assessments

CTX001 for treating severe sickle cell disease [ID4016]

An appraisal of the clinical and cost effectiveness of CTX001 for the treatment of SCD is in development. As of March 2023, there is no expected publication date posted.

Previous Reviews

Kassim, et al. (2022). "Debating the Future of Sickle Cell Disease Curative Therapy: Haploidentical Hematopoietic Stem Cell Transplantation vs. Gene Therapy."[108]

This paper discusses current and emerging curative therapies for SCD, HSCT, and gene therapy. HSCT with an HLA-matched sibling donor is a curative therapy that has been established for patients with SCD, however, this is not accessible to most patients due to a lack of matched donor. HSCT with an HLA-haploidentical donor with post-transplant cyclophosphamide and gene therapy broadens the pool of patients eligible for curative treatment. These two therapies are compared across categories such as donor availability, intensity of regimen, stem cell procurement, complications, and long-term effects.

The authors explore the pros and cons of gene therapy methods relevant to our review, lentiviral vector gene addition and nuclease editing (CRISPR/Cas9). Lentiviral vector gene addition has stable integration into the genome which can allow for long-term expression, there is no immunogenicity and can accommodate large transgenes, but can lead to potential off-target effects or mutagenesis. The pros cited for nuclease editing are that it is non-integrating, the tools are transient, and there is high editing efficiency. The cons are the requirement for DSB, potential for off-target editing, and can induce a p53 response. It is concluded that although data is currently limited, gene therapy appears to be effective and safe.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if Quantified), Likely Magnitude and Impact (if Not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	Includes caregiver impacts for modified societal perspective
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	X	X	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	N/A	X	
	Unpaid caregiver-time costs	N/A	X	
	Transportation costs	N/A	--	
Non-Health Care Sector				
Productivity	Labor market earnings lost	N/A	X	
	Cost of unpaid lost productivity due to illness	N/A	X	
	Cost of uncompensated household production	N/A	X	
Consumption	Future consumption unrelated to health	N/A	--	
Social Services	Cost of social services as part of intervention	N/A	--	
Legal/Criminal Justice	Number of crimes related to intervention	N/A	--	
	Cost of crimes related to intervention	N/A	--	
Education	Impact of intervention on educational achievement of population	N/A	--	
Housing	Cost of home improvements, remediation	N/A	--	
Environment	Production of toxic waste pollution by intervention	N/A	--	
Other	Other impacts (if relevant)	N/A	--	

N/A: not applicable

Adapted from Sanders et al. (2016).[109]

Table E2. Key Model Assumptions

Assumption	Rationale
Costs for patients who start the process of pre-transplant assessments and preparation but do not proceed with treatment are included in the model.	Preparation for transplant (e.g., assessments, tests, visits) incur additional costs that should be accounted for in the model.
The model included an evidence-based estimate of treatment failure in the first model cycle.	Where the trial data shows a proportion of patients still with VOCs after treatment, this is modeled assuming that these patients have the same rate of complications and mortality as those on standard care.
After year seven, patients on both gene therapies revert to costs and outcomes of standard care at a rate used in ICER's beta thalassemia report.[67]	The long-term durability of treatment effect is unknown. The uncertainty in the durability of treatment effect was also heard from clinical experts and patient stakeholders.
The cycle length of the model was one year.	Given the chronic nature of SCD, a cycle length of one year is expected to appropriately capture health outcomes and costs, and allow for sufficient flexibility to explore our planned sensitivity and scenario analyses.
Some patients have chronic complications at the start of the model.	Some chronic complications will have occurred by the age at the start of the model and the prevalence of these complications were sourced from published literature.
The risk of complications and death in the model were populated using data for Medicaid patients.	While some SCD patients have commercial insurance (with lower risk of complications) or Medicare (with higher risk of complications), most of the SCD patients are covered by Medicaid and, as such, the model was populated using data for Medicaid patients.
All complications (i.e., acute [except VOCs] and chronic) and death were modeled independent of each other.	We used the most relevant robust data sources to model the risk of complications and mortality, which already account for any interdependencies. As the aim is to estimate the cost-effectiveness at a population level, this approach is appropriate.
VOC rates are correlated with rates of acute and chronic complications of interest, and mortality.	We used published data on hazard ratios for the complications of interest between SCD patients with zero VOCs and those with 3+ VOCs. Similar approach was also used for mortality rates.
Treatment effect in reducing the VOCs were used to model the impact on risk of complications.	Treatment success was measured as proportion of patients without VOCs, and these patients were modelled with lower risks of acute, chronic complications and mortality based on the hazard ratios from published literature.
For chronic complications and mortality, the hazard ratios for adults are different from the adolescents to account for organ damage in the adult population.	Adult patients on SCD are assumed to already accumulate some organ damage before receiving the gene therapy and as such, the treatment effectiveness in reducing chronic complications and mortality is assumed to be lower for adults compared to adolescents (who are less likely to accumulate organ damage).
Health state disutility values were used to estimate QALY losses for acute and chronic complications.	QALY decrements for acute complications were estimated considering the short duration of the disutilities. Chronic complications were assumed to last for lifetime (i.e., until death).

Assumption	Rationale
Additive approach was used to estimate the QALYs.	Additive approach was used to estimate the health-related quality of life of patients with multiple complications, to reflect modeling of the complications independently.
For model inputs with no evidence-based specified uncertainty range, we assumed parametric distributions.	Inclusion of parameter uncertainty within one-way and probabilistic analysis allows for a reasonable characterization of uncertainty.

ICER: Institute for Clinical and Economic Review, QALY: quality-adjusted life year, SCD: sickle cell disease, VOC: vaso-occlusive crisis

Rates of Acute and Chronic Complications for Patients on Standard of Care

The transition probabilities for annual risk of complications were estimated from the incidence rates reported in published literature presented in Table E3. Most of the incidence rates were sourced from Shah et al. 2019 and Shah et al. 2020, which present the complication rates for patients insured on Medicaid.[70,73] These were supplemented with data from the previous ICER SCD report.[10] It was assumed that some adult patients have chronic complications at the start of the model, and this was estimated as prevalence of complications in commercially insured patients aged less than 18 years from Ramsey et al 2022.[76] The use of data from commercially insured patients and those less than 18 years of age would mean that the model uses a lower prevalence of chronic complications than what is likely to be observed in patients with severe SCD. The prevalence of heart failure was assumed to be zero as these patients would not receive gene therapy.

In the model, the rates of complications for adolescents are used for patients starting as adolescents and the rates change to the rates of complications for adults when the adolescents are over 18 years of age (i.e., when they become adults). For adults, the rates for adults are used throughout their lifetime. In each model cycle, the proportions of patients with acute complications are estimated by multiplying the patients alive with the risk of acute complications. For each chronic complication, in each model cycle, the proportions of patients alive without that complication are multiplied by the annual risk of that chronic complication to estimate the proportion of patients getting that complication in that model cycle. It is assumed the chronic complications last until death, and as such, in each model cycle the proportions of patients in each chronic complication are capped at the proportion of patients alive.

Table E3. Annual Incidence Rates of Complications

Complications	Incidence Rate for Adolescents*	Incidence Rate for Adults*	Source
VOCs	5.1†	5.1†	Assumption
Acute Chest Syndrome	0.0698	0.0571	Shah et al. 2019[73]
Acute Infections (Bacteremia and Sepsis)	0.017	0.038‡	McClish et al[110]
Acute Kidney Injury	0.0000	0.0006	Bradt et al. 2020[10]
Gallstones	0.0293	0.0452	Shah et al. 2019[73]
Leg Ulcers	0.0235§	0.0235§	Antwi-Boasiako et al 2020[111]
Pulmonary Embolism	0.0011	0.0208	Shah et al. 2019[73]
Stroke	0.011	0.021	Bradt et al. 2020[10]
Myocardial Infarction	0.0009	0.0069	Bradt et al. 2020[10]
Avascular Necrosis	0.0142	0.0536	Shah et al. 2019[73]
Chronic Kidney Disease	0.0143	0.0262#	Bradt et al. 2020[10]
Heart Failure	0.0075	0.0198#	Bradt et al. 2020[10]
Liver Complications	0.0067¤	0.0067 ¤	Allali et al. 2019[112]
Pulmonary Hypertension	0.0027	0.0159	Shah et al. 2019[73]
Retinopathy	0.0050	0.0050	Shah et al. 2022[113]
Chronic Lung Disease	0.0341	0.0341	Winn et al 2023[81]
Neurocognitive Impairment	0.00045	0.0034	Manwani et al. 2022
Pain and Fatigue	0.033	0.033	Bradt et al. 2020[10]

VOC: vaso-occlusive crisis

*Annual incidence rates of complications per patient.

†Annual number of VOCs.

‡Estimated as average of the different age groups.

§Prevalence of ulcers used as a proxy for annual incidence.

#Estimated as average of the 18-30 and 30-45 age groups.

¤Annual rate estimated using data from Allali et al. 2019 suggesting 6.5% prevalence over 10 year follow up.

Mortality for Patients on Standard Care

The risk of mortality for patients on standard care was estimated from the rates reported in Desai et al. 2020, based on analysis of 44,033 SCD patients insured on Medicaid.[74] Data on cumulative incidence over 13 year follow up for patients with ≥5 VOC episodes in the baseline year, who reflect the more severe SCD population, was converted into annual mortality risk assuming constant rate (i.e., exponential distribution) as shown in Table E4. For each age category, this annual mortality risk was compared to the mortality risk in general US population (at the mean age within each category) to estimate the standardized mortality ratio to be used in the model.

To estimate the mortality for a given age in the model, the general population mortality for that age was multiplied with the standardized mortality ratio for that age group i.e., standardized mortality ratio of 40.07 was applied to estimate the mortality risk for adolescents, standardized mortality ratio of 24.24 for ages 19-35, and a standardized mortality ratio of 17.48 for ages 35 and above.

Table E4. Mortality Inputs

Age Group	Mean Age	Cumulative Incidence* (95% CI)	Annual Mortality Risk	Standardized Mortality Ratio	Source
Ages 13-18	15	15.0% (11.8-18.2%)	0.0124 (0.0096, 0.0153)	40.07 (31.00, 49.46)	Desai et al. 2020[74]
Ages 19-35	25	27.3% (24.9-29.6%)	0.0242 (0.0218, 0.0266)	24.24 (21.80, 26.65)	Desai et al. 2020[74]
Ages 35+	45	45.41% (41.4-49.2%)	0.0455 (0.0403, 0.0508)	17.48 (15.47, 19.50)	Desai et al. 2020[74]

CI: confidence interval

*Over 13 year follow up.

Treatment Effectiveness on Acute Complications

The acute complication rates for the patients without VOCs after gene therapies were modeled by applying the hazard ratios reported in Table E5 to the baseline complication rates for patients on standard care (as presented in Table E3).

Bailey et al. and Herquelot et al. 2019 report the hazard ratios for patients who have 3+ VOCs compared to zero VOCs based on analysis of 15,076 patients were identified with a diagnosis of SCD using the Hospital Episode Statistics database in the United Kingdom.[114,115] Where there were data gaps, these were supplemented with data from the previous ICER report as presented in Table E5.[10] The hazard ratios for patients achieving treatment success on gene therapy were estimated as half of the inverse of the hazard ratios reported in Bailey et al. and Herquelot et al. 2019.[114,115] The reason for halving these hazard ratios is that the patients achieving treatment success on gene therapy are likely to be better than those who had zero VOCs. The "halving" to estimate the hazard ratios for patients achieving treatment success on gene therapy can be considered as being an average of the hazard ratios for the general population (likely to be close to zero) and the hazard ratios of the patients with zero VOCs.

Table E5. Treatment Effectiveness on Acute Complications

Complications	Hazard Ratio for Patients Without VOCs After Gene Therapy (95% CI)	Hazard Ratio for Patients With 0 VOCs Compared to Those With 3+ VOCs (95% CI)	Hazard Ratio for Patients With 3+ VOCs Compared to Those With 0 VOCs (95% CI)	Source
VOCs	0	--	--	Assumption
ACS	0.094 (0.076, 0.117)	0.188 (0.151, 0.233)	5.33 (4.29,6.62)	Bailey et al. 2019[114]
Acute Infections (Bacteremia and Sepsis)	0.181 (0.109, 0.299)	0.362 (0.219, 0.599)	2.76 (1.67, 4.57)	Bailey et al. 2019[114]
Acute Kidney Injury	0.131 (0.038, 0.450)	0.262 (0.077, 0.901)	3.81 (1.11, 13.0)	Bailey et al. 2019[114]
Gallstones	0.185 (0.125, 0.273)	0.370 (0.251, 0.546)	2.70 (1.83, 3.99)	Bailey et al. 2019[114]
Leg Ulcers	0.238 (0.107, 0.532)	0.476 (0.214, 1.064)	2.10 (0.94, 4.68)	Bailey et al. 2019[114]
Pulmonary Embolism	0.450 (0.231, 0.877)	0.901 (0.463, 1.754)	1.11 (0.57, 2.16)	Bailey et al. 2019[114]
Stroke	0.221 (0.190, 0.258)	0.442 (0.380, 0.515)	2.26 (1.94, 2.63)	Bradt et al. 2020[10] Shah et al. 2019[4]
Myocardial Infarction	0.388 (0.173, 0.862)	0.775 (0.346, 1.724)	1.29 (0.58, 2.89)	Bailey et al. 2019[114]

ACS: acute chest syndrome, CI: confidence interval, VOC: vaso-occlusive crisis

Treatment Effectiveness on Chronic Complications

The chronic complication rates for the patients without VOCs after gene therapies were modeled by applying the hazard ratios reported in Table E6 to the baseline complication rates for patients on standard of care (as presented in Table E3).

The hazard ratios for patients without VOCs after receiving treatment as adolescent population were estimated as half of the inverse of the hazard ratios reported in Bailey et al. 2019,[114] and the previous ICER report[10] as presented in Table 4.7. The reason for halving the hazard ratios is that the patients achieving treatment success on gene therapy are likely to be better than those who had zero VOCs. However, the hazard ratios for patients without VOCs after receiving treatment as adult population were estimated as inverse of hazard ratios (i.e., without further halving) to account for accumulated organ damage before receiving the gene therapy. Adult patients on SCD are assumed to already accumulate some organ damage before receiving the gene therapy and as such, the treatment effectiveness in reducing chronic complications is assumed to be lower for adults compared to adolescents (who are less likely to accumulate organ damage).

Table E6. Treatment Effectiveness on Chronic Complications

Complications	Hazard Ratios for Patients without VOCs After Receiving Gene Therapy as Adolescents (95% CI)	Hazard Ratios for Patients without VOCs After Receiving Gene Therapy as Adults (95% CI)	Hazard Ratios for Patients with 3+ VOCs Compared to Those with 0 VOCs (95% CI)	Source
Avascular Necrosis	0.202 (0.132, 0.309)	0.403 (0.263, 0.617)	2.48 (1.62, 3.80)	Bailey et al. 2019[114]
Chronic Kidney Disease	0.422	0.844	1.185	Bradt et al. 2020[10]
Heart Failure*	0.388 (0.173, 0.862)	0.775 (0.346, 1.724)	1.29 (0.58, 2.89)	Bailey et al. 2019[114]
Liver Complications	0.161 (0.038, 0.685)	0.322 (0.075, 1.370)	3.11 (0.73, 13.25)	Bailey et al. 2019[114]
Pulmonary Hypertension	0.192 (0.105, 0.352)	0.385 (0.211, 0.704)	2.60 (1.42, 4.75)	Bailey et al. 2019[114]
Retinopathy†	0.321	0.641	1.56	Bailey et al. 2019[114]
Chronic Lung Disease‡	0.163 (0.106, 0.250)	0.326 (0.212, 0.500)	3.07 (2.0, 4.72)	Bailey et al. 2019[114]
Neurocognitive Impairment§	0.190 (0.089, 0.407)	0.380 (0.177, 0.813)	2.63 (1.23, 5.64)	Bailey et al. 2019[114]
Pain and Fatigue	0.255	0.509	--	Assumed to be average of the hazard ratios

CI: confidence interval, VOC: vaso-occlusive crisis

*Hazard ratio for cardiac complications used as a proxy for hazard ratio for heart failure.

†Hazard ratio for retinal vascular occlusion from sensitivity analysis of Bailey et al. 2019[114] as main analysis suggested increased risk for those with 0 VOCs.

‡Hazard ratio for cardiomegaly from Bailey et al. 2019[114] used as a proxy for hazard ratio for chronic lung disease.

§Hazard ratio for central nervous system complications from Bailey et al. 2019[114] used as a proxy for hazard ratio for neurocognitive impairment.

Treatment Effectiveness on Mortality

The mortality rates for the patients without VOCs after gene therapies were modeled by applying the hazard ratios reported in Table E7 to the baseline mortality rates for patients on standard care (estimated based on rates as presented in Table E4).

The relationship between the number of VOCs experienced in the previous year and mortality was sourced from Desai et al. 2020 who report a hazard ratio of 3.23 (2.95-3.53) using unadjusted extended Cox models for patients with ≥5 VOCs compared to patients with <2 VOCs.[74] The use of this study is deemed reasonable given the higher mortality rates for standard care patients based on data for patients with ≥5 VOC episodes in the baseline year.

The hazard ratios for patients without VOCs after receiving treatment as adolescent population were estimated as half of the inverse of the hazard ratios reported in Desai et al. 2020.[74] The reason for halving these hazard ratios is that the patients achieving treatment success on gene therapy are likely to be better than those who had zero VOCs. The hazard ratios for patients without VOCs after receiving treatment as adult population were estimated as inverse of hazard ratios (i.e., not halved) to account for account for accumulated organ damage before receiving the gene therapy.

Table E7. Treatment Effectiveness on Mortality

	Hazard Ratios for Adolescents With No VOCs After Gene Therapy (95% CI)	Hazard Ratios for Adults With No VOCs After Gene Therapy Compared to Severe SCD Patients (95% CI)	Hazard Ratios for Patients With ≥5 VOCs vs. Those With <2 VOCs (95% CI)	Source
Base-Case Analysis	0.155 (0.142, 0.169)	0.310 (0.283, 0.339)	3.23 (2.95; 3.53)	Desai et al. 2020[74]

CI: confidence interval, VOC: vaso-occlusive crisis

Disutilities

Disutilities of complications were sourced from Sullivan et al. 2006[69] as reported in Table E8. The QALY losses for acute complications were estimated considering their short duration and the QALY losses for chronic complications were estimated assuming they last for lifetime (i.e., until death). An additive approach was used to estimate the QALYs to reflect modeling of the complications independently.

Table E8. Disutilities Associated with Acute and Chronic Complications

Complications	Disutility	Source
VOCs*	-0.23	Anie et al. 2012,[68]
ACS*	-0.0412	Sullivan et al 2006[69]
Acute Infections (Bacteremia and Sepsis)*	-0.05	Assumption
Acute Kidney Injury*	-0.0527	Sullivan et al 2006[69]
Gallstones†	-0.0288	Sullivan et al 2006[69]
Leg Ulcers†	-0.0272	Sullivan et al 2006[69]
Pulmonary Embolism*	-0.0198	Sullivan et al 2006[69]
Stroke‡	-0.0524	Sullivan et al 2006[69]
Myocardial Infarction‡	-0.0409	Sullivan et al 2006[69]
Post Stroke	-0.0524	Sullivan et al 2006[69]
Avascular Necrosis	-0.0380	Sullivan et al 2006[69]
Chronic Kidney Disease	-0.0603	Sullivan et al 2006[69]
Heart Failure	-0.0635	Sullivan et al 2006[69]
Liver Complications	-0.0567	Sullivan et al 2006[69]
Pulmonary Hypertension	-0.0428	Sullivan et al 2006[69]
Retinopathy	-0.0498	Sullivan et al 2006[69]
Chronic Lung Disease	-0.0667	Sullivan et al 2006[69]
Neurocognitive Impairment	-0.0494	Sullivan et al 2006[69]
Pain and Fatigue	-0.05	Assumption

ACS: acute chest syndrome, QALY: quality-adjusted life year, VOC: vaso-occlusive crisis

*Assumed to last for two weeks.

†Assumed to last for three months.

‡Assumed to last for half year.

Costs

The model also included upfront costs of $114,227 associated with the gene therapies after inflating the costs used in the beta thalassemia ICER report to 2022 values.[67] This included $3,023 for the work-up costs, $18,967 for pre-transplant costs, $89,419 for transplant costs, and $2,818 for the costs of infertility treatments due to myeloablative conditioning. In line with the beta thalassemia ICER report,[67] monitoring costs of $8,653 per year were also included for the first three years for those receiving gene therapy. Patients who start the process of pre-transplant assessments and preparation but do not proceed with gene therapy, estimated as 16.3% based on the data from the trials that seven out of 43 patients did not proceed to gene therapy, are assumed to incur the work-up costs and pre-transplant costs, and these costs were included in the gene therapy arms.

Standard of Care Costs

The costs of standard of care were estimated from Gallagher et al 2022,[116] who present the five-year costs of severe SCD for Medicare, Medicaid and commercially insured patients. We used the costs of outpatient pharmacy, outpatient other services, and outpatient visits for Medicaid patients as they are considered to be a reasonable estimate of standard of care costs (as they include the

costs of hydroxyurea, chronic blood transfusions, and iron chelation therapies). These five-year costs were inflated to 2022 costs using the personal consumption expenditure health care indices, and then divided by five to estimate the annual costs as shown in Table E9 below.

We assumed that the standard of care costs would be eliminated for patients with successful gene therapy treatment (i.e., patients without VOCs). While some outpatient visits and services may still exist for successfully treated gene therapy patients, we have used an optimistic assumption on eliminating these standard of care costs for patients successfully treated with gene therapy.

Table E9. Standard of Care Costs

	Five-Year Costs (in 2018 Values)	Five-Year Costs (in 2022 Values)	Annual Costs (in 2022 Values)	Source
Outpatient Pharmacy	$24,721	$27,168	$5,434	Gallagher et al 2022[116]
Outpatient Other Services	$32,714	$35,953	$7,191	Gallagher et al 2022[116]
Outpatient Visits	$4,062	$4,464	$893	Gallagher et al 2022[116]
Total Costs of Standard of Care	$61,497	$67,585	$13,517	Gallagher et al 2022[116]

Non-Drug Costs

The costs for complications in the model were populated using most relevant data from published literature and inflated to 2022 costs using the personal consumption expenditure health care indices. These costs were used consistently across treatments evaluated in the model. A recent systematic review by Baldwin et al. 2020[77] was used to identify the sources that best reflect the costs for US SCD patients, with most of the costs from the previous ICER SCD report.[10] The costs of VOCs were sourced from Shah et al 2020[70] who report the average cost of VOCs for Medicaid patients across different settings (i.e., inpatient, emergency room, outpatient, and office), as these costs were considered to most likely reflect the cost of VOCs (rather than assuming that all VOCs are costed assuming an inpatient visit).

The costs for acute complications were modeled as one-off costs while the costs for chronic complications are modeled as annual costs, as shown in Table E10. Whilst there are studies that present annual "overall" health costs after a complication, these are not considered appropriate for inclusion in the model. This is because these estimates include all health care costs (i.e., SCD standard of care costs, costs of complications and non-SCD related health care costs) while the model uses costs specific to the complications, and using the overall annual health care costs for complications results in double counting and overestimation of costs of complications.

Table E10. Costs of SCD-Related Complications

Complications	Costs (In 2019 Values)	Costs (In 2022 Values)	Source
VOCs	$5,335	$5,762	Baldwin et al. 2020[77]
ACS	$26,299	$28,403	Baldwin et al. 2020[77]
Acute Infections (Bacteremia and Sepsis)*	--	$11,354	Song et al 2019[117]
Acute Kidney Injury	$8,205	$8,861	Bradt et al. 2020[10]
Gallstones*	--	$14,328	Song et al 2019[117]
Leg Ulcers*	--	$8,110	Song et al 2019[117]
Pulmonary Embolism	$13,879	$14,989	Khoury et al 2020[118]
Stroke†	$57,780	$62,403	Bradt et al. 2020[10]
Myocardial Infarction	$53,458	$57,735	Bradt et al. 2020[10]
Post Stroke	$9,807	$10,592	Bradt et al. 2020[10]
Avascular Necrosis*	--	$14,869	Song et al 2019[117]
Chronic Kidney Disease	$20,708	$22,365	Bradt et al. 2020[10]
Heart Failure	$32,505	$35,106	Bradt et al. 2020[10]
Liver Complications	$16,919	$18,273	Hirode et al 2020[119]
Pulmonary Hypertension	$19,343	$20,891	Bradt et al. 2020[10]
Retinopathy	$13,595	$14,683	Nguyen et al 2022[120]
Chronic Lung Disease	$10,367	$11,196	Ur Rehman et al 2020[121]
Neurocognitive Impairment	$11,687	$12,622	Bradt et al. 2020[10]
Pain and Fatigue	$4,398	$4,750	Bradt et al. 2020[10]

ACS: acute chest syndrome, VOC: vaso-occlusive crisis

*Costs estimated by multiplying the coefficients of the regression equations in Song et al 2019[117] with the 2022 standard of care costs, and subtracting the standard of care costs to estimate the additional costs associated with the complications. Also, these costs are not inflated as they are based on 2022 standard of care costs.

†Additional costs of $77,951 are incorporated on top of $62,403 for stroke in adolescent patients in line with the previous ICER SCD report.[10]

Description of evLY Calculations

The evLY considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1) First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[122]
2) We calculate the evLY for each model cycle.
3) Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained within the cycle.
4) The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5) The total evLY for a cycle is calculated by summing steps 3 and 4.

6) The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7) The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Description of Optimistic and Conservative Scenarios

Optimistic and conservative assumptions regarding the benefit of treatment with lovo-cel and exa-cel were performed to reflect the uncertainty in the clinical data. Details of the scenarios are provided below.

Table E11. Assumptions for Optimistic and Conservative Scenarios Analysis Results

	Base Case	Optimistic Scenario	Conservative Scenario
Treatment Waning (0.27% Reverting)	After 7 years	Never	After 7 years
Additional Utility for Patients without VOCs on Gene Therapy	0.05	0.05	0.03
Hazard Ratio Multipliers for Acute Complications	0.5	0.5	1
Hazard Ratio Multipliers for Adolescents for Chronic Complications	0.5	0.5	1
Hazard Ratio Multipliers for Adults for Chronic Complications	1	0.5	1
Hazard Ratio Multipliers for Adults for Death	1	0.5	1

VOC: vaso-occlusive crisis

Results of Deterministic Analysis

Tables E12 and E13 present the breakdown of the results from the deterministic analysis.
Table E12 presents the breakdown of the costs. The costs of standard care relate to the costs of outpatient pharmacy, outpatient other services, and outpatient visits. The costs of preparation relate to the preparatory work and monitoring costs associated with gene therapy. The costs of acute complications and chronic complications are those associated with treating the acute and chronic complications of SCD, respectively.

Table E12: Breakdown of the Costs from the Deterministic Analysis from Health Care Perspective

	Costs of standard care	Costs of preparation	Costs of treatment	Costs of acute complications	Costs of chronic complications	Total costs
Undiscounted costs						
Lovo-cel or Exa-cel	$11,073	$143,416	$2,000,000	$64,863	$1,475,972	$3,695,324
Standard Care	$316,075	$-	$-	$799,271	$1,384,482	$2,499,828
Discounted costs						
Lovo-cel or Exa-cel	$7,258	$142,683	$2,000,000	$38,897	$637,670	$2,826,507
Standard Care	$213,564	$-	$-	$539,833	$736,405	$1,489,801

Table E13 presents the breakdown of the QALYs. As the model uses additive approach to estimate the QALYs to reflect modeling of the complications independently, the total QALYs are estimated by subtracting the QALYs lost due to complications from the QALYs gained due to uncomplicated SCD. The QALYs gained due to uncomplicated SCD relate to the QALYs gained assuming there are no complications. The QALYs lost due to acute complications and chronic complications, are the QALYs lost associated with disutilities of the acute and chronic complications of SCD, respectively.

Table E13: Breakdown of the QALYs from the Deterministic Analysis from Health Care Perspective

	QALYs gained	**QALYs lost due to acute complications**	**QALYs lost due to chronic complications**	**Total QALYs**
Undiscounted QALYs				
Lovo-cel or Exa-cel	32.86	-0.05	-4.71	28.11
Standard Care	18.71	-1.09	-4.59	13.03
Discounted QALYs				
Lovo-cel or Exa-cel	18.45	-0.03	-2.04	16.38
Standard Care	12.64	-0.73	-2.46	9.44

Results of Probabilistic Sensitivity Analysis

Figures E1 and E2 present the scatterplot of the incremental costs and QALYs for lovo-cel and exa-cel, respectively. There is greater spread in the incremental QALYs for exa-cel (Figure E2) due to the greater uncertainty around the treatment success rate of exa-cel. Tables E14 and E15 present the percent of iterations that were beneath thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY gained from both the health care system perspective and the modified societal perspective for lovo-cel and exa-cel, respectively.

Figure E1. Scatterplot for Lovo-Cel (Health Care System Perspective)

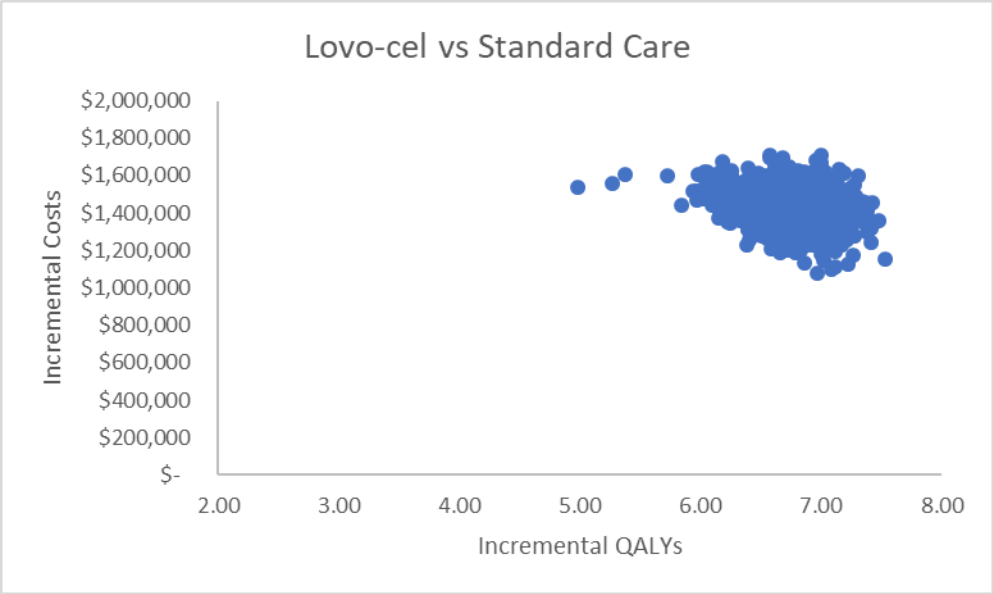


Figure E2. Scatterplot for Exa-Cel (Health Care System Perspective)

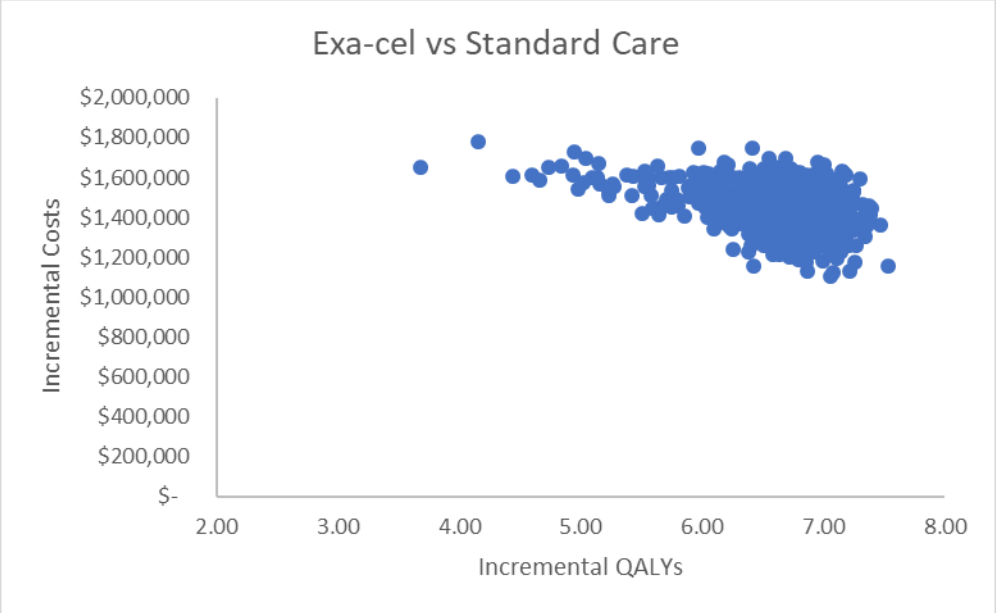


Table E14. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: lovo-cel vs. Standard of Care

	Probability of being Cost Effective at $50,000 per QALY Gained	Probability of being Cost Effective at $100,000 per QALY Gained	Probability of being Cost Effective at $150,000 per QALY Gained	Probability of being Cost Effective at $200,000 per QALY Gained
Health Care System Perspective				
lovo-cel	0%	0%	0%	29%
Modified Societal Perspective				
lovo-cel	0%	0%	7%	87%

QALY: quality-adjusted life year

Table E15. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: exa-cel vs. Standard of Care

	Probability of being Cost Effective at $50,000 per QALY Gained	Probability of being Cost Effective at $100,000 per QALY Gained	Probability of being Cost Effective at $150,000 per QALY Gained	Probability of being Cost Effective at $200,000 per QALY Gained
Health Care System Perspective				
exa-cel	0%	0%	0%	23%
Modified Societal Perspective				
exa-cel	0%	0%	5%	75%

QALY: quality-adjusted life year

Threshold based price assuming outcomes based agreements

In this scenario, it was assumed that the costs of gene therapy for patients who still have VOCs will be borne by the company. The threshold based prices for this scenario are presented in Table E16.

Table E16. Results of threshold based price assuming outcomes based agreement

Treatment	Placeholder Price*	Unit Price to Achieve $50,000 per QALY Gained	Unit Price to Achieve $100,000 per QALY Gained	Unit Price to Achieve $150,000 per QALY Gained	Unit Price to Achieve $200,000 per QALY Gained
Health Care System Perspective					
lovo-cel or exa-cel	$2,000,000	$1,040,000	$1,400,000	$1,750,000	$2,110,000
Modified Societal Perspective					
lovo-cel or exa-cel	$2,000,000	$1,260,000	$1,620,000	$1,980,000	$2,330,000
Treatment	**Placeholder Price***	**Unit Price to Achieve $50,000 per evLY Gained**	**Unit Price to Achieve $100,000 per evLY Gained**	**Unit Price to Achieve $150,000 per evLY Gained**	**Unit Price to Achieve $200,000 per evLY Gained**
Health Care System Perspective					
lovo-cel or exa-cel	$2,000,000	$1,090,000	$1,490,000	$1,900,000	$2,300,000
Modified Societal Perspective					
lovo-cel or exa-cel	$2,000,000	$1,310,000	$1,710,000	$2,120,000	$2,530,000

QALY: quality-adjusted life year; evLY: equal value life year
*Excludes workup and preparation, transplant, or post-transplant monitoring costs. Unit price represents the placeholder value for the full acquisition cost of lovo-cel or exa-cel per patient

F. Potential Budget Impact: Supplemental Information

Methods

Potential budget impact was defined as the total differential cost of using each gene therapy rather than standard of care for people living with severe SCD in the US, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. The five-year timeframe was chosen given the potential for cost offsets to accrue over time and to provide a more realistic uptake assumption on the number of patients treated with lovo-cel and exa-cel.

This potential budget impact analysis included the estimated number of people in the US who are likely to be eligible for treatment. Those eligible may be different from the number of people who may ultimately choose to receive either lovo-cel or exa-cel. To estimate the size of the potential candidate populations for treatment, we used manufacturer data submissions and literature and consider between 20,000 and 25,000 people living with severe SCD in the US to be eligible for lovo-cel or exa-cel.[82-84] We used the upper end of this range (25,000) and divide this estimate in two for those eligible for lovo-cel (N=12,500) and separately, exa-cel (N=12,500) as per ICER's Reference Case. For the purposes of this analysis, we assume that 20% of these patients would initiate treatment in each of the five years, or 2,500 patients per year per gene therapy.

ICER's methods for estimating potential budget impact are described in detail elsewhere.[123,124] The intent of our approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Once estimates of budget impact are calculated, we compare our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation, this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2022-2023, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $777 million per year for new drugs.

Results

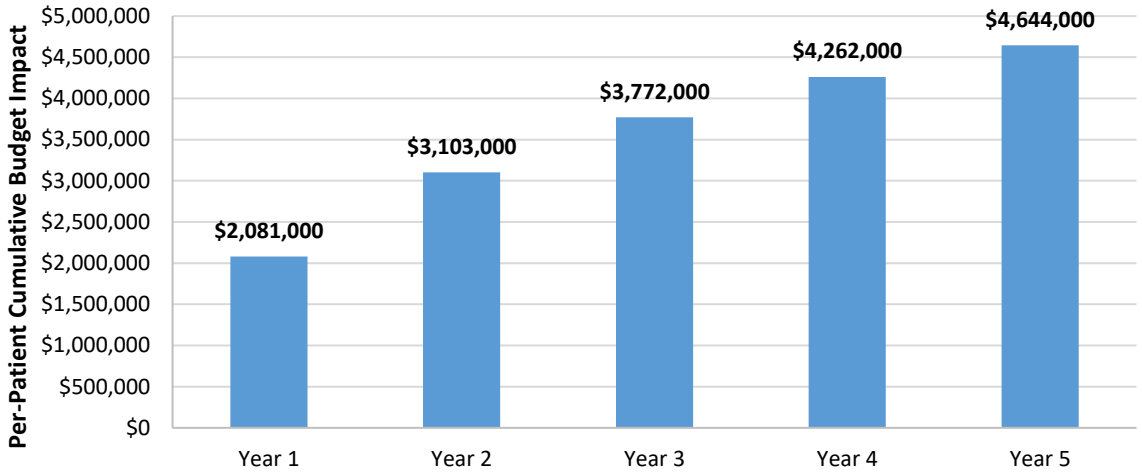
Table F1 illustrates the average annual per-patient budget impact calculations for lovo-cel or exa-cel over 5 years at placeholder acquisition price ($2 million [per treatment course]), and the prices to reach $150,000, $100,000, and $50,000 per QALY ($1.70 million, $1.35 million, and $1.00 million per treatment course, respectively) when comparing lovo-cel or exa-cel to standard of care. Note that the average annual per-patient budget impact must be multiplied by five in order to capture the cumulative budget impact of lovo-cel or exa-cel for a cohort of US patients living with severe SCD over five years (see Figure F1 for an additional visualization regarding cumulative budget impact at lovo-cel's or exa-cel's placeholder acquisition price).

Table F1. Average Annual Per-Patient Budget Impact Calculations Over a Five-year Time Horizon

	Average Annual Per-Patient Budget Impact			
	Placeholder Acquisition Price	**$150,000/QALY**	**$100,000/QALY**	**$50,000/QALY**
lovo-cel or exa-cel vs. Standard of Care	$929,000	$792,000	$632,000	$472,000

QALY: quality-adjusted life year

Figure F1. Per-Patient Cumulative Budget Impact of lovo-cel or exa-cel over Five Years Assuming 20% Uptake Per Year at Placeholder Acquisition Price of $2 Million



G. Supplemental Policy Recommendations

Payers

Coverage Criteria: General

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy: see Cornerstones of "Fair" Drug Coverage: Appropriate Cost-Sharing and Utilization Management Policies for Pharmaceuticals.

- If an initial request for coverage is denied, access to a peer-to-peer call should be rapid. In many clinicians' experience, gaining access to peer-to-peer discussion is onerous. Peer-to-peer calls facilitate the communication of individual patients' unique clinical characteristics and need for therapy. The physician peer should be knowledgeable in the management of SCD.

Drug-Specific Coverage Criteria

Coverage Criteria: Eligibility and Exclusion Criteria

- **Diagnosis:** It is reasonable for plans to include documentation of an eligible genotype in coverage criteria. Genotype corresponds well with degree of phenotypic severity. Genotypes eligible for the pivotal trials were βS/βS, βS/β0, and βS/β+ for lovo-cel, and βS/βS and βS/β0 for exa-cel. Clinical experts argued that βS/β+ patients can have severe phenotype and therefore this genotypic variant should be considered reasonable to cover for treatment with both gene therapies. Because of adverse events in patients with co-occurring alpha-thalassemia, it is reasonable and expected that these patients will be excluded from eligibility.

- **Age:** Payers will follow any labelled age restrictions for lovo-cel and exa-cel. If the FDA includes an age restriction, it seems likely that they will limit treatment to patients aged 12 or older, consistent with the clinical trial criteria. Trials are ongoing for both gene therapies among younger patients (ages 2 – 12). Even before potential expansion of an initial label to include younger children, clinical experts suggested that they would be likely to identify patients under aged 12 whose families desire gene therapy before further organ damage can occur, so payers will need to consider exceptions and actively monitor the evolving evidence base on younger pediatric patients. Alternatively, payers may adopt a broader age

range for coverage and delegate decisions regarding appropriate patient selection to clinical experts at Center of Excellences.

- **Severity of SCD:** Following clinical trial eligibility language, the FDA is likely to approve gene therapies for patients with "severe" SCD, however the FDA may or may not define severity beyond noting the specific genotypic variants included. If the FDA does not include its own definition of severity, payers are likely to use clinical trial eligibility criteria related to the number and severity of vaso-occlusive events or crises (VOEs/VOCs) to define a threshold needed for coverage.

  Different definitions of VOEs and VOCs were used in the pivotal trials for the two gene therapies (see Table 1 below). Both trials used a two-year look-back period but stipulated slightly different numbers (e.g. four severe VOEs over two years vs. two VOCs per year over two years). If payers choose to use these thresholds in coverage, they should minimize the documentation burden by allowing clinician attestation. But neither definition is preferred by the clinical experts participating in the policy roundtable. These experts were concerned that any definition would be arbitrary and may exclude some patients for whom gene therapy would be very advisable given the nature of a smaller number or frequency of VOEs/VOCs. An example presented by one of the clinical experts participating in the policy roundtable was a pediatric patient with SCD and a history of stroke who now is undergoing chronic lifelong exchange transfusions, which additionally prevents VOCs/VOEs. Clinical experts felt this patient would be an ideal candidate for gene therapy but would not meet the technical specifications of the severity threshold in the clinical trials. The hope was also expressed that patients who choose to self-manage their VOEs at home despite great pain should not be denied coverage because they do not use the ER often enough to qualify.

  Therefore, as noted earlier, payers should consider the tradeoffs of adopting the specific clinical trial eligibility criteria in coverage versus an approach that relies on clinician discretion when these treatments are delivered at specialized SCD Centers of Excellence.

Table G1. Definitions of Primary Study Outcomes

	exa-cel CLIMB-121[41]	lovo-cel HGB 206[38]
VOC/VOE	Not defined/measured in trial	VOE is defined as an episode of acute pain with no medically determined cause other than a vaso-occlusion and included acute episodes of pain, ACS, acute hepatic sequestration, acute splenic sequestration, and acute priapism
Severe VOC/VOE	Severe VOC is defined as any one of the following: • Acute pain event that requires a visit to a medical facility and administration of pain medications (opioids or IV NSAIDs) or RBC transfusions • ACS, as indicated by presence of new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever • Priapism lasting >2 hours • Splenic sequestration	Severe VOE is defined as any one of the following: • A visit to a hospital or ED that exceeded 24 hours • At least 2 visits to day unit or ED during a 72-hour period (with both visits requiring IV treatment) • Priapism episode lasting more than 2 hours and leading to a medical-facility visit

ACS: acute chest syndrome, ED: emergency department, IV: intravenous, NSAID: non-steroidal anti-inflammatory drug, RBC: red blood cell, VOC: vaso-occlusive crisis, VOE: vaso-occlusive event

- **Availability of HSCT:** Clinical trial eligibility required that patients not have accessibility to a sibling-matched HSCT as first-line therapy. HSCT also offers a potential cure for SCD and has a far longer clinical track record. Clinical experts suggested that the new gene therapies would offer the advantage of avoiding immunosuppression over the longer term, but that most clinicians today would view a sibling-matched HSCT as a reasonable option prior to considering gene therapy. Attestation that a patient does not have a willing matched donor should suffice for coverage of gene therapy.

- **Appropriate usual care with hydroxyurea:** Hydroxyurea is the bedrock of appropriate usual care for patients with SCD, and the clinical trials required that patients have severe SCD while being treated with hydroxyurea. Clinical experts did not view it as unreasonable for payers to require attestation that patients have experienced inadequate control of VOE/VOCs while being treated with hydroxyurea.

- **Exclusion criteria**: Within the list of exclusion criteria for entry into the clinical trials, clinical experts emphasized that history of stroke should not be included as an exclusion for insurance coverage. Patients with a history of stroke were excluded from the clinical trials most likely to reduce the risk of short-term adverse events that could be difficult to ascribe to treatment as opposed to the underlying condition, but clinical experts argued that these patients are at high risk for further strokes and therefore have substantial opportunity to benefit from gene therapy.

H. Public Comments

This section includes summaries of the public comments prepared for the CTAF Public Meeting on July 27, 2023. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Three speakers did not submit summaries of their public comments.

A video recording of all comments can be found here. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Anjulika Chawla, MD, bluebird bio
Senior Medical Director, Clinical Research and Development

My name is Anjulika Chawla and I lead the lovo-cel clinical development program at bluebird bio. I am also a practicing pediatric hematologist-oncologist for more than 20 years. I have dedicated my career to the care of individuals and families impacted by sickle cell disease, and today I am more hopeful about their future than ever before.

Sickle cell disease is a complex and progressive disease that impacts every aspect of life. People living with sickle cell disease often face frequent vaso-occlusive crises, mounting and irreversible organ damage over time, profoundly diminished quality of life, and ultimately a life cut short by decades—not years, but decades.

As bad as that sounds, from my experience supporting and learning from patients, the reality is worse. The pain and fatigue that people with SCD endure and manage has impacts beyond the physical into mental health and psychosocial functioning.

I have worked with children who were bullied and ostracized because they were small, weak, and had frequent absences from school. I have worked with young adults who after multiple, unpredictable and long hospitalizations isolate themselves and be isolated by others as they were a burden to their friends, families, and co-workers. I have met parents who refused opioids despite excruciating pain, due to concern they would jeopardize their ability to care for their children, and others who live in constant fear they will not survive long enough to see their children grow up.

Even with all the advances in the last few decades, people living with sickle cell disease need and deserve options that can have a transformative effect on their health and quality of life; options that enable them to determine their destiny, rather than have it defined by their disease.

As the most deeply studied gene therapy in development for SCD, we are confident in the value lovo-cel can deliver—first and foremost to patients and their families, but also more broadly to the healthcare system and society.

In our studies, we observed that after treatment, the production and persistent presence of the modified anti-sickling hemoglobin A in the red blood cells of all patients to last patient visit as far out as 8 years. Also shown is improved total hemoglobin and complete resolution of vaso-occlusive events in most patients. These results signal the potential to improve disease trajectory without the need for ongoing disease modifying therapies.

We see that these physical and clinical improvements are translating into improvements in quality-of-life, particularly the intensity of pain experienced by the individual and the overall impact of pain on fundamental aspects of daily life. Further, we are seeing improvements in the ability to work and on work productivity. As ICER's assessment recognizes, all of these data points are consistent with a potentially transformative benefit for patients.

As we discuss the potential value of lovo-cel for SCD, I cannot help but think of patients who have died waiting for a one-time therapy option. I think of the time, effort, and sacrifice of these sickle cell warriors, their families and friends – not to mention the money spent in the medical care that couldn't keep them alive or free from vaso-occlusive pain.

I think of Deron, age 20, an engaging college student with his own YouTube channel, who voted for Obama proudly from the intensive care unit and succumbed from a stroke a few weeks later.

I think of Paula, age 24, an effervescent and kind woman despite having severe chronic pain and recurrent vaso-occlusive pain, a hip replacement, and kidney failure. She had over 20 admissions annually for the last few years of her life before dying of a severe vaso-occlusive event.

I think of Ray, age 26 and a father, who had a matched sibling donor but was unable to proceed with transplant and died suddenly from acute chest syndrome.

We need more options for treatment for people for sickle cell disease, and for those with severe disease we need them now. The decision of whether or not to pursue this option should be in the hands of the patient, their family, and their healthcare provider, armed with information of the known risks and benefits, as well as an understanding of what is yet unknown.

We are grateful to the sickle cell community who has been with us on this journey for close to a decade. We are both humbled and proud to be part of this new wave of potential one-time treatment options that this community both needs and deserves.

In closing, I want to thank ICER for their thoughtful consideration and recognizing the value of lovo-cel. I also want to thank you for your time, and for the opportunity to share my perspective.

Dr. Chawla is a full-time employee of bluebird bio.

Dr. Chawla collaborated with Real chemistry, a third-party entity to directly compose public comments at ICER's public meeting.

Jaime Rubin Cahill, MA, MPH, Vertex Pharmaceuticals
Vice President, HEOR

Sickle cell disease (SCD) is a life-shortening disease marked by painful blood vessel blockages, known as vaso-occlusive crises (VOCs) that cause severe pain, organ damage and a range of other debilitating acute and chronic complications. These profound impacts are exacerbated by systemic healthcare inequities faced by people with SCD, including longer emergency room wait times, undertreatment of pain, and stigmas associated with the disease. The economic burden of SCD on the healthcare system is also profound, with recent estimates of lifetime costs for people experiencing recurrent VOCs totaling $4.2-$6.2 million. The economic model produced by ICER underestimates these costs, by using the lowest available VOC event cost in the model. To accurately value transformative therapies for this disease, healthcare costs must be appropriately considered.

Currently available treatment options require chronic therapy and do not alleviate key aspects of SCD burden, especially painful VOCs – we now have the ability to change that outlook. Last month, we presented data on 35 patients with SCD who received exa-cel who were followed from 2 to 39 months. Seventeen of these patients were evaluable for the primary and key secondary endpoint at the time of the data cut. Sixteen of 17 achieved the primary endpoint of freedom from severe VOCs for at least 12 months. The one patient who did not meet this primary endpoint did not experience any hospitalizations related to severe VOCs, a key secondary endpoint. Moreover, all of the additional 18 patients dosed with exa-cel were severe VOC-free in the evaluable period, with mean total follow-up of 8.55 months. These results are in stark contrast to the approximately 5 VOCs that patients experience per year based on natural history data. Patients also reported substantial, clinically relevant improvements in health-related quality of life across a range of domains, and the safety profile was generally consistent with myeloablative conditioning and autologous stem cell transplant. Together, these data demonstrate clear differentiation of exa-cel versus current standard of care.

The clinical and safety profile is further bolstered by data in a different disease area, transfusion dependent beta thalassemia (TDT), where 48 patients have been treated with exa-cel using the same gene editing and manufacturing process and have been followed for up to 43.7 months with almost 90% of evaluable patients achieving transfusion independence.

These data on exa-cel are unique and cannot be directly compared to data on lovo-cel primarily because of the differences in how events were captured in their clinical trials. The exa-cel trial assessed severe VOCs, whereas the lovo-cel trial assessed severe vaso-occlusive events (VOEs). Even though the two endpoints sound similar, they are very different. Severe VOC is more rigorous and inclusive of the events experienced by patients and results in a higher bar to achieve the primary endpoint. For example, severe VOCs include any pain event that requires a visit to a

medical facility and administration of pain medications or transfusions. In contrast, a severe VOE includes only the events that required a hospital or emergency department visit that were at least 24 hours, or at least 2 visits to a day unit or emergency department during a 72-hour period. As a reminder, 100% of patients treated with exa-cel met our key secondary endpoint of hospitalization free for 12 consecutive months, which is a closer analogue to the severe VOE endpoint.

In addition to the differences in the clinical trial endpoints, exa-cel has a unique mechanism of action. Exa-cel uses CRISPR-Cas9 technology, a non-viral and extremely precise tool to edit relevant stem cells. Biologically, there is no known mechanism whereby these permanently gene edited cells could revert back to their prior form, and therefore lifelong durability of treatment effect is expected – durability we've demonstrated in the data reported so far. Other gene therapies, including lovo-cel, rely on viral vectors that randomly insert into the genome to edit cells. 20-years of data on lentiviruses have shown there can be a risk of malignancies caused by these random insertions. In contrast, extensive preclinical characterization of exa-cel has shown zero evidence of off-target editing, and with exa-cel there is no virus, and no random insertional mutagenesis. We have dosed over 80 patients who have up to 43.7 months of follow-up in SCD and TDT and have observed no malignancies.

We are excited about the possibilities that exa-cel can bring to transform the lives of people with SCD. We are at the cusp of truly making a difference for the sickle cell community and are committed to continuing this journey with our fellow sickle cell warriors.

Jaime Rubin Cahill is a full-time employee of Vertex Pharmaceuticals.

Maggie Jalowsky, Sick Cells
Director of Advocacy

Sick Cells is a national advocacy organization for sickle cell disease. Thank you for the opportunity to provide comment on ICER Final Report.

Throughout our engagement with ICER during this review, we have noted several key limitations to ICER's ability to reflect patient-centric dimensions within the cost-effectiveness modeling. The first concern is that this model does not bring a truly comprehensive view of what matters most to individuals living with the disease. Capturing patient-centric dimension of value is crucial to properly demonstrate the value new innovations can have. For sickle cell, many patient-important outcomes are omitted from ICER's cost-effectiveness model despite strong and repeated emphasis on their importance from patients, clinicians, and manufacturers.

Since 2019, Sick Cells has been working to identify what matters most to those living with the disease through quantitative and qualitative methods. In a recent project, we worked with a multi-stakeholder group to prioritize value elements for sickle cell disease. From this project, the top two value elements were ranked as mental health effects, such as depression and anxiety, and overall quality of life. Neither of these are included as complications in the model, indicating the inability to reflect the full patient experience and priorities in the value calculation.

ICER notes that their discussions with experts lead to the selection of the conditions used in the model, however, there is a lack of transparency into who was consulted and if patients and caregivers were included as experts to weigh in on these modeling decisions. Sick Cells served as a liaison during ICER's focus group sessions with 4 patients and 4 caregivers, however, those sessions primarily informed the Patient Perspective paragraphs of the report and did not include members of ICER's economic modeling team.

The second limitation was the use of inappropriate health state utility score data to reflect patient experience. Health-related quality of life weights that are used to generate the QALYs incorrectly assume "uncomplicated SCD" to be 0.8 utility value. The reference study, Anie 2012, did not measure uncomplicated SCD and only captured QOL through the EQ-5D one week after patients were discharged from the hospital after having a severe pain event. Anie notes, "Patients were not completely pain-free on discharge and importantly at 1-week follow-up." Health utility scores derived from this study are not appropriate or sufficient evidence to support a conclusion as a baseline for how individuals experience the quality of life without pain.

The third concern is the perpetuation of existing disparities using ICER's current Value Assessment Framework. As stated by Dr. Power-Hays and Dr. McGann in their 2020 article, "There may be no population of patients whose health care and outcomes are more affected by racism than those with sickle cell disease." ICER shares realities such as poor healthcare quality, poor clinical

communications, barriers to access, and poor uptake in their report, which shows how racism manifests across healthcare for sickle cell. Without the use of an equity-informative economic model, ICER is unable to adequately account for these disparities in their base-case results, leading to concern that recommendations from this analysis will contribute to further inequities.

While the public meeting deliberation discussed equity considerations, the impact of this discussion is limited. Evidence from experts, such as AMCP, show that payers do not prioritize factors like equity in decision-making unless value elements can be quantified within the cost effectiveness analysis. The ICER CTAF committee were also asked to vote on if there is adequate evidence to demonstrate health benefit. Meaningful data that clearly defines and measures effectiveness in this framework requires years of investment in time, money, partnership, and academic expertise, which has not been available to the sickle cell disease community for generations. In ICER's approach to be objective and consistent across all assessments, cost-effectiveness findings are unable to address the severe unmet need that exists for some conditions, such as sickle cell disease. ICER is retrofitting a framework that is not suitable for sickle cell disease, which perpetuates the mistreatment these patients know all too well.

Thank you for this opportunity to comment. We look forward to our continued partnership with ICER and other stakeholders working to improve lives with sickle cell.

Sick Cells has received sponsorship funding and charitable contributions in excess of $5,000 from companies developing in sickle cell. These funds are not in any way connected to, or conditioned upon, any past, present or future prescribing, purchasing, or recommending product manufactured or marketed by these companies.

Maggie Jalowsky holds status as an employee of Sick Cells, which has received sponsorship funding and charitable contribution from companies developing in sickle cell (>25%).

Tesha Samuels, Journey to ExSCellence
Patient Advocate

You can search the globe to hear the stories of Sickle Cell Warriors, and although there will be similarities, not one of them are the same. My Sickle Cell journey began at the age of 2 when after numerous infections, colds, and fevers, from infancy-parental instincts prevailed! My mother was able to get the official diagnosis of Sickle Cell Anemia. Now that we knew what to call it, we didn't necessarily know what to do that information. It wasn't too long before my family knew that raising me would be much different than what they anticipated. At 7, I had an aplastic anemia crisis which started with fevers and cold symptoms and therefore not taken as seriously as it should have been. By the time, it was realized, it was almost too late for me. The missed days of school became greater as the years rolled by and the pain went from some of the time, to most of the time, and finally by 13, it was all the time. At this age, I suffered a Transient Ischemic Attack which left me as a pre-teen having to regain strength of affected side. From that experience, there was concern that this would happen again if monthly blood transfusions weren't started immediately. Up to then, I was taking Penicillin each day, pain medicine as needed, and yet the quality of life was only what I could make of it based on how I felt each day. At 14, I'm left to deal with typical teen thoughts and emotions, all while juggling a schedule of every 3-4 weeks needing a "tune-up"! This involved a multi-hour clinic visit to receive blood transfusions each month. Only to realize that it only did not keep me from having pain crises and being in and out of the hospital for weeks. Pain so excruciating my routine was to have water and pain medication at least 30 minutes before starting the day. By 15, I was missing so much school, the family advocated for me to be homeschooled by a professional to provide flexibility should something happen yet continue my studies. At 16, I suffered an Acute Chest Crisis, which was so painful, they placed me in an induced coma for weeks. It took 9 months to regain all that I had lost. In that time, my family grappled with the thought that I may need implanted pain medication pump and possibly wheelchair bound. I left Kennedy Krieger Hospital and returned home with a goal to make sure I graduated on time. God granted that prayer and I was able to walk across the stage to receive my high school diploma.

As an adult with Sickle Cell Disease, things didn't get much better even when my smile and zest for life hid how I felt most days. Frequent and long hospital stays threatened my academic and professional life many times. It even thwarted my plans to have a family with my husband.

After 3 years of weekly visits to remove the iron that overloaded my body after 21 years of monthly blood transfusions, I was told me there wasn't more she could offer treatment wise, and would soon need dialysis.

I contacted National Institutes of Health to see what if anything they could do for me. I was tired, fed up and dare I say desperate to get off this never-ending cycle of pain.

I made the decision to become a Blue Bird Bio trial participant for an autologous gene therapy transplant. This process meant that I would undergo heavy doses of chemotherapy which temporarily harmed the esophageal lining, gave me mouth sores, and eradicated further chances for pregnancy. With all that, I was not deterred from this mission. I didn't make or take this decision likely but if 3 months of in-person treatment, 15 years of follow-ups even had a chance of eradicating this disease, I knew I had to do it! Faith is what helped me through the disease and it led me to the decision.

What you see today is Tesha Samuels who through all my struggles and yes, triumph's I have been granted a chance to begin a new chapter. It has become evident to my mind and now I truly understand His true plan for my life.

Please consider the impact to the quality of life this may have to a warrior, who just wants a chance to experience this type of existence. Thank you for listening and for your consideration.

Nothing to disclose.

Elinam Joe Tsogbe
Patient

My name is Elinam Joe Tsogbe. I would like to begin by thanking you for allowing me to participate in the public comment section of the meeting.

A brief overview of my history:

I was born with Sickle Cell Disease (SCD), Hemoglobin SS, in Togo, West Africa. I was diagnosed at the age of 8 months and have endured a series of complications from Sickle Cell Disease, ranging from gallbladder removal to a total hip replacement.

I wish to highlight some of the challenges I have faced as a young adult before the age of 25, along with the average expenses one might accrue over the years. The information below does not encompass details of treatments such as Exchange Blood Transfusions (RBC Exchanges) that I underwent in my 30s prior to the CRISPR Gene Editing Trial with Vertex.

Between the ages of 31 and 35, I received exchanged transfusions once or twice a month and underwent fluid and IV medication administration 2 to 3 times weekly when I was not admitted, all while trying to manage work and other activities.

The following analysis is based on my experiences from the age of 16 to 25.

Cost and Damages of Sickle Cell Disease (SCD) for Patients Living in the United States:

1. High Healthcare Expenditure:

The patient's average of 14 hospitalizations per year, with a minimum stay of 10 days each time, results in a total of 140 hospital days annually.

Costs include hospital charges, medical procedures, medications, and specialized care during hospital stays.

Estimated 25-Year Cost: With the high hospitalization rate in the United States, the cumulative cost over 25 years can range from $700,000 to $1,400,000 or more, taking into account the cost of healthcare services.

2. Hip Replacement Surgery:

The patient underwent a total hip replacement before the age of 20, incurring significant surgical and post-operative costs.

Additional costs may arise from complications or future revision surgeries.

3. Diminished Quality of Life:

Chronic pain and fatigue lead to limitations in daily activities.

Impaired physical and emotional well-being affect social life and mental health.

Decreased productivity and missed educational and employment opportunities.

4. Potential Organ Damage:

Increased risk of organ damage due to repeated Vaso-occlusive events (e.g., lungs, liver, kidneys, brain).

Long-term complications may lead to organ failure and necessitate costly organ transplants.

Estimated 25-Year Cost: The cost of managing organ damage and potential transplants can range from $500,000 to $1,000,000 or more over 25 years.

5. Increased Susceptibility to Infections:

SCD patients are more susceptible to infections due to compromised immune function.

Frequent infections require additional medical interventions and increased healthcare costs.

6. Economic Burden on Families:

-Families of SCD patients experience financial strain due to ongoing medical expenses.

- Time off work to care for the patient or accompany them to treatments affects household income.

7. Reduced Life Expectancy:

SCD significantly reduces life expectancy, leading to premature mortality.

Early deaths result in lost potential contributions to the workforce and society.

8. High Societal Costs:

Cumulative costs of managing SCD for a significant patient population burden healthcare systems and society.

Health resources directed towards managing SCD could be utilized more efficiently with curative approaches.

In conclusion:

For a patient like myself who has lived in the United States with Sickle Cell Disease, underwent a total hip replacement before the age of 20, and experienced an average of 14 hospitalizations per year, the estimated cumulative costs over 25 years can range from $1,350,000 to $2,800,000 or more. This substantial financial burden, combined with the challenges faced by patients, their families, and society, underscores the urgent need for a curative approach like gene therapy. Investing in gene therapy for SCD can not only significantly improve patients' quality of life, as it has for me, but also reduce the overall economic burden on both patients and healthcare systems in the long run.

Gene therapy has provided me with a renewed lease on life.

Elinam Joe Tsogbe collaborated with Sick Cells to directly compose public comments delivered at the ICER public meeting.

I. Conflict of Interest Disclosures

Tables I1 through I3 contain conflict of interest (COI) disclosures for all participants at the July 27, 2023 Public meeting of CTAF.

Table I1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Francesca Beaudoin, MD, PhD, MS, Senior Medical Advisor, ICER*	**Dmitriy Nikitin, MSPH**, Senior Research Lead, Evidence Synthesis, ICER*
Jon Campbell, PhD, MS, Senior Vice President for Health Economics, ICER*	**Becca Piltch, MPP**, Program Associate, ICER*
Kelsey Gosselin, MA, Program Manager, ICER*	**Steve Pearson, MD, MSc**, President, ICER*
Avery McKenna, BS, Associate Research Lead, ICER*	**David Rind, MD, MSc**, Chief Medical Officer, ICER*
Emily Nhan, BA, Senior Research Assistant, ICER*	**Praveen Thokala, MASc, PhD**, Senior Research Fellow, University of Sheffield*

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Table I2. CTAF Panel Member Participants and COI Disclosures

Participating Members of CTAF*	
Ralph Brindis, MD, MPH, Clinical Professor of Medicine, UCSF*	**Joy Melnikow, MD**, Professor Emeritus, University of California Davis*
Robert Collyar, Patient Advocate, Patient Advocates in Research*	**Elizabeth Murphy, MD, Dphil**, Professor of Medicine, UCSF*
Rena Fox, MD, Professor of Medicine, UCSF*	**Kathryn Phillips, PhD**, Professor, UCSF*
Kimberly Gregory, MD, MPH, Vice Chair OB/GYN, Cedars Sinai Medical Center*	**Ann Raldow, MD, MPH**, Associate Professor, UCLA*
Paul Heidenreich, MD, MS, Professor, Stanford University School of Medicine*	**Rita Redberg, MD**, Professor of Medicine, UCSF*
Jeffrey Hoch, MA, PhD, Professor, University of California Davis*	**Alex Smith, MD, MS, MPH**, Professor of Medicine, UCSF*
Jeff Klingman, MD, Chair of Neurology, Kaiser Permanante NCAL*	**Joanna Smith, LCSW, MPH**, CEO, Healthcare Liaison*

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table I3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Cecelia Calhoun, MD, MPHS, MBA, Assistant Professor of Medicine, Hematology, Yale University School of Medicine; Medical Director, Sickle Cell Program, Smilow Cancer Hospital	Nothing to disclose.
Jaime Rubin Cahill, MA, MPH, Vice President, HEOR, Vertex Pharmaceuticals	Jaime Rubin Cahill is a full-time employee of Vertex Pharmaceuticals.
Elle Cole, BA, Certified Sickle Cell Medical Advocate, Cleverly Changing, LLC	Nothing to disclose.
Michelle Gourdine, MD, SVP, CVS Health; Chief Medical Officer, CVS Caremark	Dr. Gourdine is an employee of CVS Health. She receives equity interest in excess of $10,000 Agilon Health, had status as a Agilon Health board director, as a Horizon BCBS NJ board director, and at the University of Maryland Medical System.
Jimi Olaghere, Patient Expert	Nothing to disclose.
Patrick McGann, MD, PhD, Director, Lifespan Comprehensive Sickle Cell Center, Rhode Island Hospital and Hasbro Children's Hospital; Associate Professor of Pediatrics and Medicine, Alpert Medical School of Brown University	Dr. McGann received monetary value in excess of $5,000 after serving on a Novartis Safety Advisory Board.
Clark Paramore, MSPH, Head of Value Demonstration, bluebird bio	Clark Paramore is a full-time employee of bluebird bio
John Watkins, PharmD, MPH, BCPS, Residency Program Director, Premera Blue Cross	John Watkins is a full-time employee at Premera Blue Cross.