

KEY FINDINGS

Intervention	Evidence Rating	Annual WAC*	Health-Benefit Price Benchmark	Change from Annual Price to Reach Threshold Price
lovotibeglogene autotemcel (“lovo-cel”, bluebird bio)	At least an incremental net benefit compared with standard of care (B+)	Placeholder price: \$2M	\$1.35M to \$2.05M	Not applicable
exagamglogene autotemcel (“exa-cel”, Vertex Pharmaceuticals and CRISPR Therapeutics)	Comparable, result in incremental net benefit, or result in substantial net benefit when evaluated against standard of care (C++)	Placeholder price: \$2M	\$1.35M to \$2.05M	Not applicable

*WAC: wholesale acquisition cost; based on placeholder prices

“Sickle cell disease can affect nearly every organ system in the body, and severe sickle cell disease affects nearly every aspect of a person’s life. In the US, it is a disease that heavily affects the American descendants of those who were forcibly brought here as slaves. As such the US government and US payers have special obligations to ensure access to these new transformative gene therapies for sickle cell disease, and US manufacturers have special obligations to price such therapies low enough to facilitate broad access so as to maximize benefits for this population that has suffered historic harms and ongoing discrimination.”

– ICER’s Chief Medical Officer, David Rind, MD

THEMES AND RECOMMENDATIONS

- 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.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

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.

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. 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. Associated health care costs are high, with the total economic costs of SCD estimated at \$2.98 billion per year in the US. 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.

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

Clinical Analyses

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.

Economic Analyses

LONG-TERM COST EFFECTIVENESS

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.

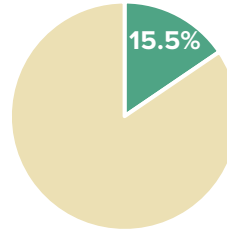
Economic Analyses

POTENTIAL BUDGET IMPACT

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. 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.

Exa-cel or Lovo-cel



Percent of eligible patients with sickle cell disease that could be treated in a given year before crossing the ICER potential budget impact threshold

Public Meeting Deliberations

VOTING RESULTS

For adolescents and adults with severe sickle cell disease (SCD) who do not have access to, or cannot receive, hematopoietic stem cell transplantation (HSCT) from a matched sibling or haploidentical donor:

- A majority of panelists (13-1) found that current evidence is **adequate** to demonstrate a net health benefit for exagamglogene autotemcel (exa-cel) when compared to standard of care (i.e., hydroxyurea, chronic blood transfusions, pain medication, iron chelation).
- A majority of panelists (13-1) found that current evidence is **adequate** to demonstrate a net health benefit for lovotibeglogene autotemcel (lovo-cel) when compared to standard of care (i.e., hydroxyurea, chronic blood transfusions, pain medication, iron chelation).
- All panelists (14-0) found that current evidence is **not adequate** to distinguish the net health benefit between exa-cel and lovo-cel.

During their deliberations, panel members also weighed potential benefits and disadvantages beyond the direct health effects, and broader contextual considerations. Voting highlighted the following as particularly important for payers and other policymakers to note:

- The acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability;
- The magnitude of the lifetime impact on individual patients of sickle cell disease;
- The likelihood that these new treatments will improve patients' broader ability to achieve major life goals related to education, work, or family life;
- The likelihood that these new treatments will improve caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life;

Public Meeting Deliberations

- The likelihood that these new treatments will improve patients' ability to manage and sustain treatment given the complexity of regimen;
- The likelihood that these new treatments will meaningfully address society's goal of reducing health inequities.

Consistent with ICER's process, because there is no firm estimate yet of a potential launch price for both treatments, the panel did not take separate votes on the treatments' long-term value for money.

About ICER

The Institute for Clinical and Economic Review ([ICER](#)) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public

hearings through three core programs: the California Technology Assessment Forum ([CTAF](#)), the Midwest Comparative Effectiveness Public Advisory Council ([Midwest CEPAC](#)) and the New England Comparative Effectiveness Public Advisory Council ([New England CEPAC](#)). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer.org).