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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 31 participants, only seven participants had 12 months of follow-up available for review, and all seven 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 degree of risk of gene therapies in the real world, particularly over the long-term. In particular, there were two instances in which the FDA placed a partial clinical hold on lovo-cel due to safety concerns surrounding hematologic malignancies, including two cases of acute myeloid leukemia that resulted in death. 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. At a placeholder price of $2 million for each therapy, we found the following results from the health care system perspective and the societal perspective.

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

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

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 2((3)pc 2-1039 -D.2 d-0i)

populations of people

3. Comparative Clinical Effectiveness

loa

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--

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 3.5 severe VOEs per year in the two years prior to trial enrollment.[37]

splenic sequestration. This was measured from the 60 days after a person's last red blood cell transfusion up to two years after exa-cel infusion.

The mean incidence of severe VOC per year during the two-year period before screening was 3.9 (range: 2-9.5). Of the 31 participants enrolled, seven participants had 12 months of follow-up at the February 2022 data-cutoff. All seven participants remained severe VOC-free.[39]

Additional Patient-Important Outcomes

We are aware that quality of life measures including a weekly pain scale, the EuroQol quality-of-life scale, EQ-5D-Youth scale, functional assessment of cancer therapy-bone marrow transplant, 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 additional for 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: 15-37) and 32 (range: 23-74) days, respectively. The median time to last red blood cell transfusion was 19 days (range: 11-52).

Hemoglobin levels were assessed in the entire study population, without regard to the duration of follow-up. However, owing to the limited follow-up and the small size of the sample, the number of participants evaluated at each time point decreased, with only a single patient being evaluated after 24 months. At baseline, the mean hemoglobin level was 9.1 g/dL (n=30). The hemoglobin level increased to 12.1 g/dL at three months (N=25) and remained consistent through month 15 (n=6). However, by month 30, the total hemoglobin concentration had declined to 10.6 g/dL (n=1) (see Supplement Table D8).[43]

BCL11A is a transcription factor that suppresses fetal hemoglobin in adult cells and editing BCL11A results in increased expression of fetal hemoglobin.[44] Fetal hemoglobin is a modulator of disease severity in SCD. The proportion of edited BCL11A alleles in bone marrow CD34+ HSPCs was 86.6% (n=7) and was 76% (n=17) in peripheral blood mononuclear cells.[43]

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.[45-47] Fetal hemoglobin accounted for 5.1% of the overall hemoglobin at baseline (n=30). The mean proportion of fetal hemoglobin

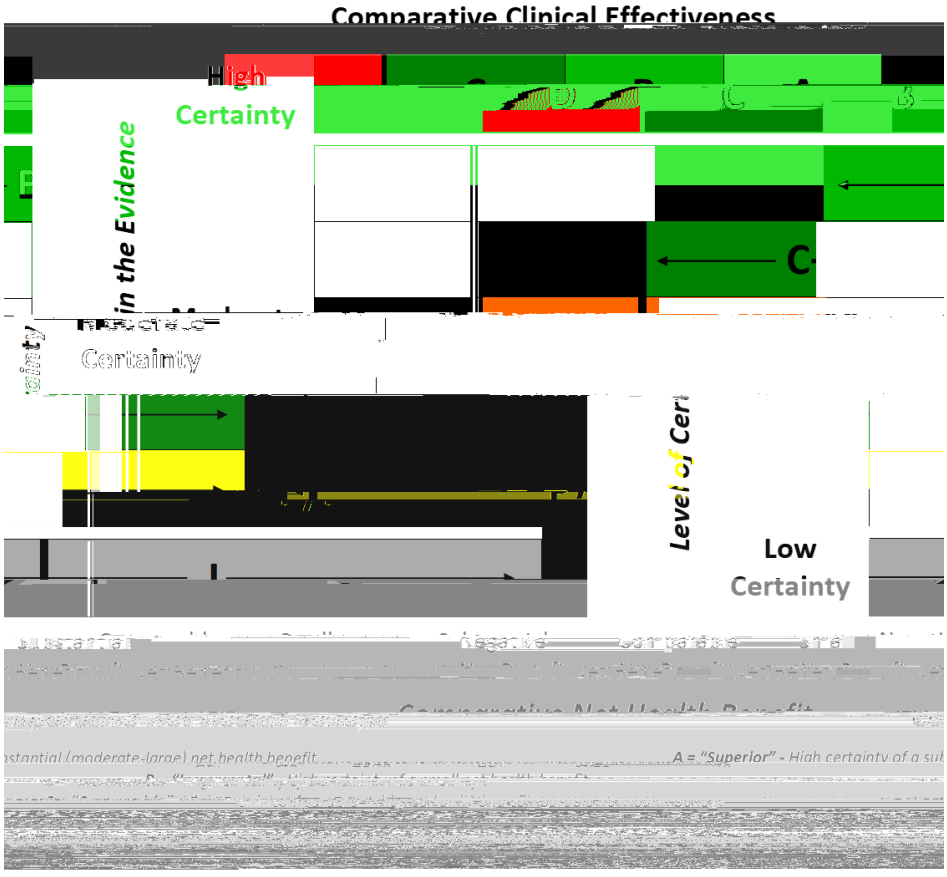
Although trials only included patients who were unable to undergo sibling-matched allogenic HSCT, it is uncertain whether clinicians and patients will routinely prefer HSCT in patients with a matched sibling donor.

The two gene therapies have substantially different mechanisms of action. Differences in the definitions of outcomes (VOEs vs. VOCs, severe vs. 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



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+) 3 (a-8 (l)-6.1 ( )]T0.2 (o)-9.3 (v14.3 (r)-1.2 ((n)-0.8 (w 12lt)-3.4 (i)-5.2

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

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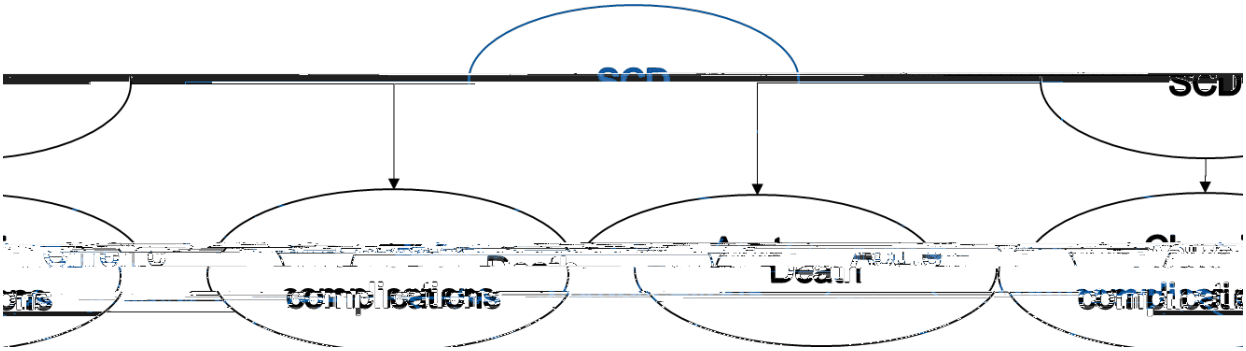
trial data on VOCs and other supporting outcomes was used to estimate the treatment effect on these complications.

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.

Assumption	Rationale
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 coste aote the fp-2 ndec 9 (

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 vs. 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

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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[61] as reported in Supplement Table E15. 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.

t

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 incree9 (o)-6.3 (f)1 (.9 1-3v.2 (f)-2n61(C)1.8-5.2 (f) (o)-9.os.8 (t)7.3n4.2.729 -1

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 ininiS-2 (4(e)]TJ0 Tp/6MeT ()-10.2 (l-7 (s)-9.8 (.)3.4 (r)-19 (a)5.3 (e)-7 (d)-)-3.7 (5n)4.9e(i)-ET/Span1 >>BD

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							

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 (n=7), 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 vs. 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
*Placeholder value based on analyst estimates.

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 $250,000 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	$211,000	$236,000	$186,000	$15,900
Optimistic	Standard of care	$152,000	$167,000	$137,000	$14,500
Conservative	Standard of care	$269,000	$279,000	$225,000	$16,700
Modified Societal Perspective					
Base Case	Standard of care	$180,000	$201,000	$158,000	$13,500
Optimistic	Standard of care	$127,000	$140,000	$115,000	$12,200
Conservative	Standard of care	$231,000	$239,000	$193,000	$14,300

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

*Placeholder value based on analyst estimates.

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 lovo-cel acquisition alone.

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

6. Health-Benefit Price Benchmarks

ICER does not provide health-benefit price benchmarks as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the threshold prices section of this draft report will match the health-benefit price benchmarks that will be presented in the next version of this report.

Further, as stated in ICER's Single and Short-Term Therapy Adaptation to the Value Assessment Framework, shared savings threshold analyses for estimating treatment price may be presented and may be considered as guides to ICER's pricing if the following two criteria are met:

1) A large percentage of the traditional value-based price comes from cost offsets of comparator (e.g., standard of care) therapy.
2) Comparator therapy price is not known to meet common cost-effectiveness thresholds.

For this assessment, the modeled comparator (e.g., standard of care without costly

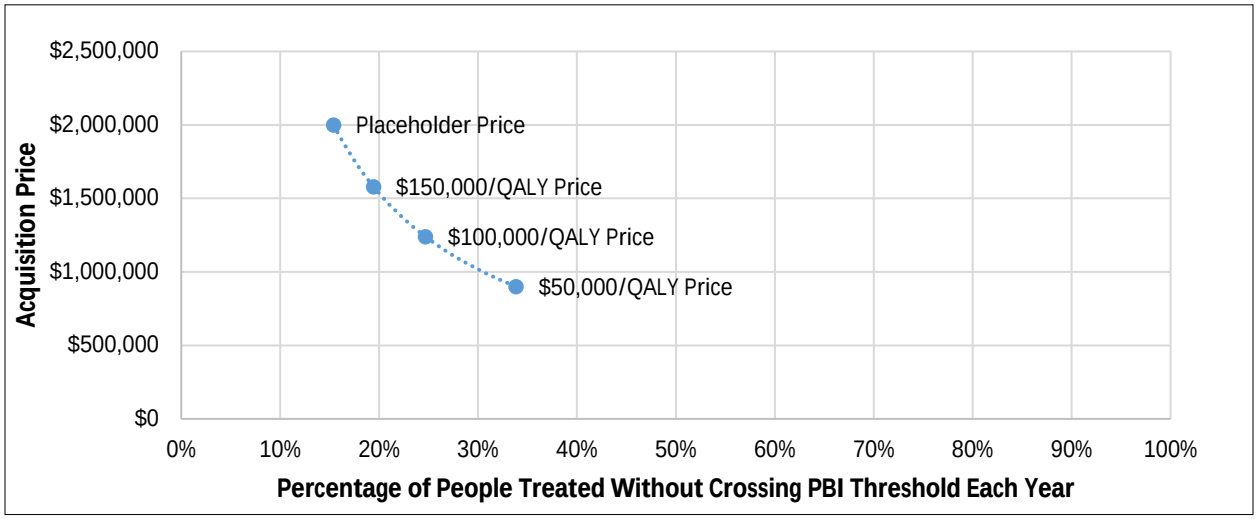
7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost

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

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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[76]: 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[77]: 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[78]: P

, ^ **t thalassemia**[82]: Occurs in patients who inherit one sickle cell gene and one beta thalassemia gene resulting in reduced production of HbA.

HbSC[82]: One inherited sickle cell gene ("S") and one abnormal Hb gene ("C"), which typically presents as milder anemia.

HbSD, HbSE and HbSO[82]: One inherited sickle cell gene ("S") and one gene from an abnormal type of Hb ("D,""E," or "O").

HbSS[82]

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

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.

In

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.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

Population, Interventions, Comparators, Outcomes, Timing, Settings

Section and Topic	Item #	Checklist Item

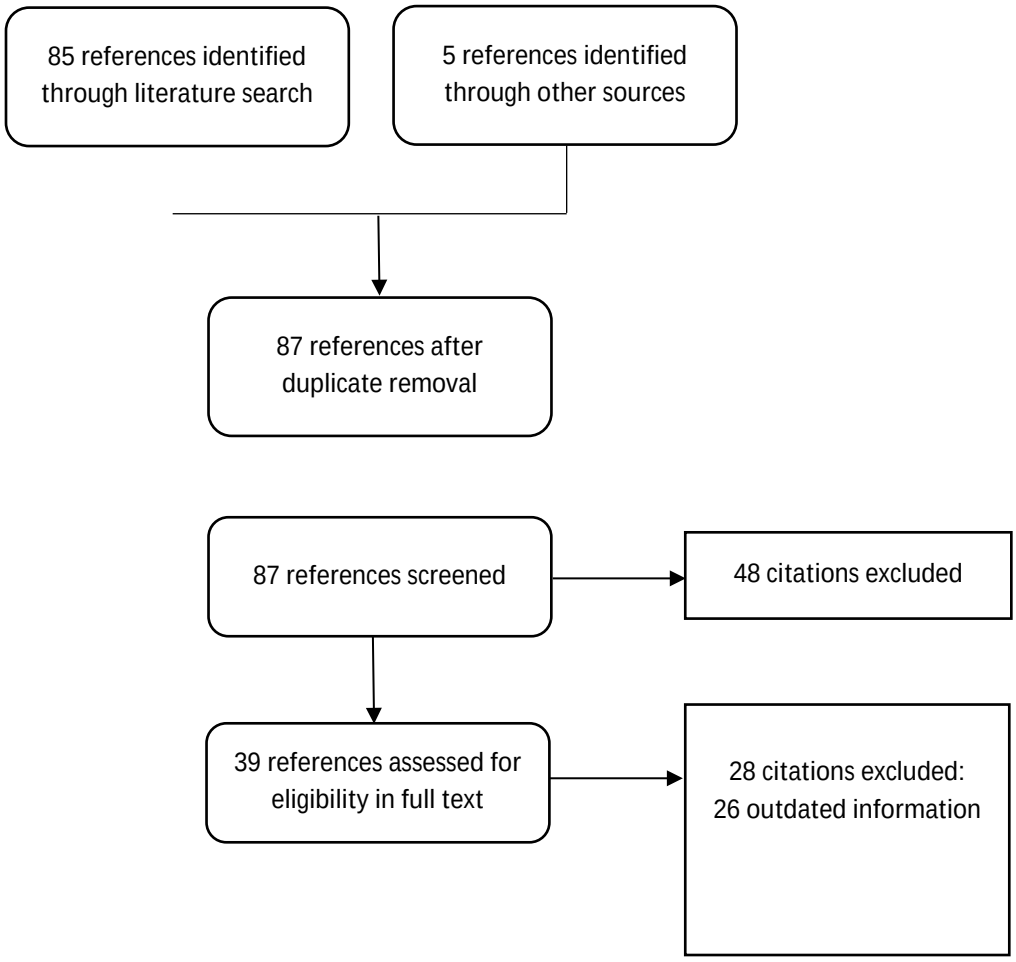
Data Sources and Searches

Procedures for the sy

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

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 heal2 (t)-3.3 BT 0 0 7.76 0 Td( )Tj-0.005 Tc 0.008 Tw 0.229 0 Tdb (d)-0.8 (e)-7 (n)-0.8 (e)-3 (f)-2.2 (i)-5.1 (t)

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[37,38,57] NCT02140554	Phase I/II, single-arm, open-label, nonrandomized trial Follow-up: 24 months post-transplant	Modified Group C (HDCE subgroup): Patients with severe SCD with -			

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
Magrin 2022[54] NCT02151526	nonrandomized trial Follow-up: 24 months post-				

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
					-Time to engraftment [up to 2 years after infusion] -Frequency and (years after infusion) [Infusion 1 to 7 years after infusion]

Table D7. Efficacy Outcomes: lovo-cel[37,38,57]

HGB-206

HGB-206			
Outcome	**Timepoint**	**N**	**Iovo-Cel: Group C**
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.

Table D9. Patient-Reported Outcomes: Lovo-cel[41]

	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	

Table D10. Safety: Lovo-cel[37]

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)
Treatment-	**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)

Table D11. Safety: exa-cel[39]

D3. Ongoing Studies

Table D12. 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 anticoagher		

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 briefl2 (e)-4 (N)-1.8e

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, vis (a)41-2.1 (t)ois (a)41-2.751

Assumption	Rationale
Additive approach was used to estimate the QALYs.	Additive approach was used t96 -0 0.001n7 (a)-51.2 (i)-p3.4 (i3-6

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[6]

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.[66] 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 W š] v š • t] š Z H ñ 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[66]

CI: confidence interval, VOC: vaso-occlusive crisis

Disutilities

Disutilities of complications were sourced from Sullivan et al. 2006[61] as reported in Table E8. The QALY losses for acute complications were estimated considering their short duration and the QALY

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[104]
Outpatient Other Services	$32,714	$35,953	$7,191	Gallagher et al 2022[104]
Outpatient Visits	$4,062	$4,464	$893	Gallagher et al 2022[104]
Total Costs of Standard of Care	$61,497	$67,585	$13,517	Gallagher et al 2022[104]

Table E10. Costs of SCD-Related Complications

Complications	Costs (In 2019 Values)	Costs (

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.s (e (t)1L)3 Tw ari.(ac)6.3 (n91s)-4.8[(6)0.6 ())]T53 (t)-3.4 (o)-9.2 (T3 .3 (r)-10(e)-7 ((e)-7 2 (d)-0.L(a)

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

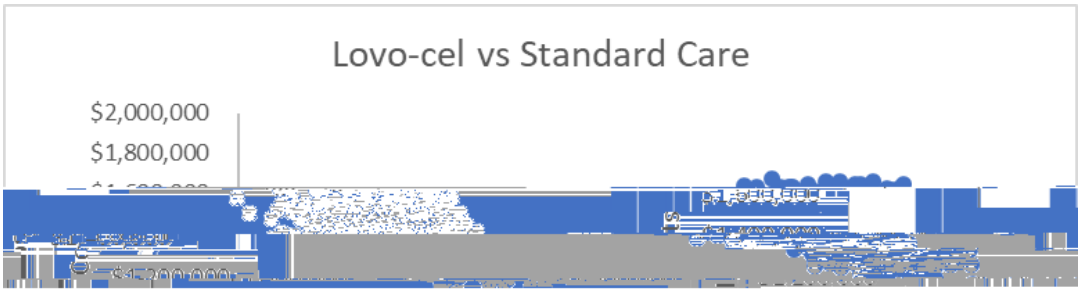
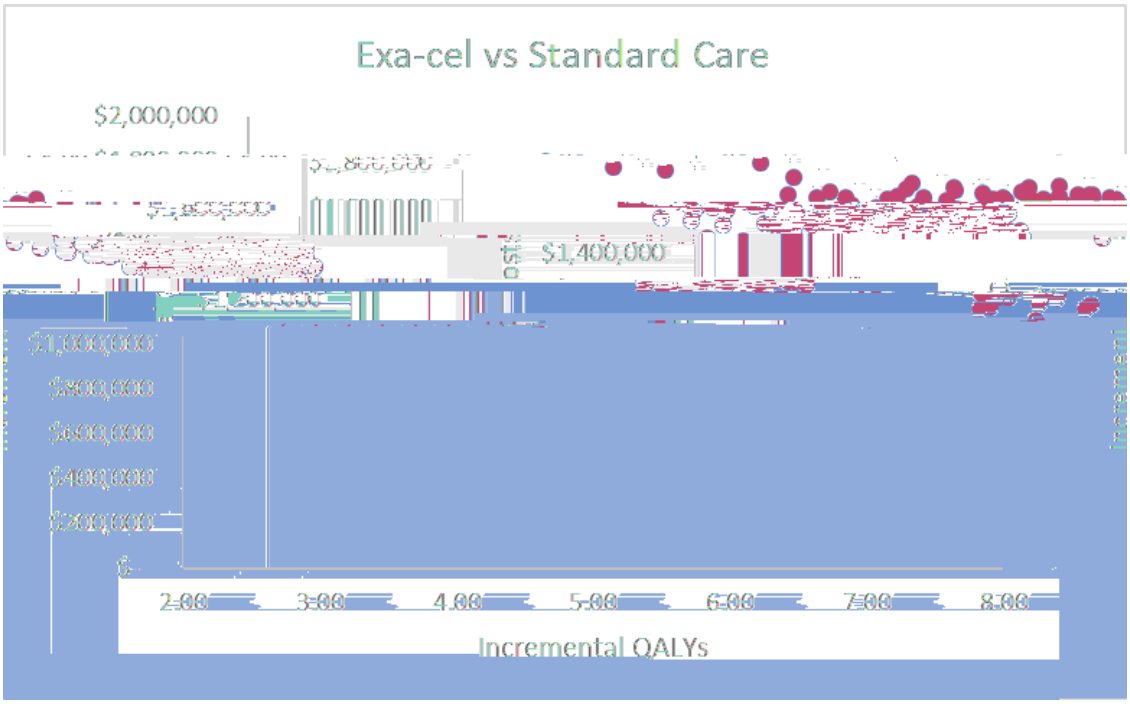


Figure E2. Scatterplot for Exa-Cel (Health Care System Perspective)



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

(u)94.2 pl631ultadeicn costs (including drug costs) minus 0l631u(E)-7.007-0.912,78.12 (21de[])-10.1R)-30.7Td(9.91)3.3 (n)-3 (rd)631u(Ta)5

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