May 1st, 2023

Institute for Clinical and Economic Review
Two Liberty Square Boston, MA 02109
RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear Dr. Pearson,

We appreciate the opportunity to offer comments in response to the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report on Gene Therapies for Sickle Cell Disease (SCD). **Sick Cells** is a national patient advocacy organization that aims to elevate the voices of the SCD community. We advocate for improving value assessments for sickle cell disease through a transparent and collaborative approach with representation of patient and caregiver perspectives and methods that support equity. Sick Cells works with patients, researchers, health economists, payers, and providers to find the right approach to measuring the cost and value for SCD. Based on this expertise, we offer the following recommendations on the report:

Section 2: Background

- We would like to thank ICER for supporting two community focus groups and incorporating community feedback into the Background section to help other stakeholders better understand the realities of this disease.
- The report acknowledges existing SCD treatments other than hydroxyurea – l-glutamine, crizanlizumab, voxelotor – and notes that they are "generally reserved for people with persistent or frequent painful episodes despite hydroxyurea therapy." Given that the population of focus for the economic evaluation would meet this treatment description (i.e., individuals with severe SCD reoccurring VOCs), we recommend ICER include these three treatments in the standard of care (SOC) definition for SCD. There should be an explanation if ICER does not include these treatments as SOC.
- Additionally, please provide background information about iron chelation products – deferasirox, deferiprone, and deferoxamine. Iron chelation is a standard practice for individuals with SCD receiving regular blood transfusions to reduce the risk of iron overload. Iron overload can cause severe complications such as liver disease and heart problems.

Section 3: Patient and Caregiver Perspectives

We applaud ICER for summarizing the patient and caregiver perspectives, however, we note that several considerations represented in this section are currently missing from the economic modeling used in this report. We offer the following recommendations to represent patient and caregiver perspectives in the model:

- Time required for people with SCD and caregivers to do activities related to health care, such as finding a medical provider or negotiating with health insurance companies, should be included in the modeling.
- ICER should include out-of-pocket expenditures and indirect costs such as childcare, transportation, and managing pain crises at home in the modeling.
- ICER discussed the "broad appreciation" of impacts needed to measure value in SCD.

ICER should apply a broader set of HTA methods and include societal perspective inputs in the base-case analysis.
- The impact of discrimination, stigma, and racial bias should be accounted for in the model through quantitative empirical measures.
- ICER should include a quantified description of when patients' health deteriorated so that potential benefits outweigh potential risks.
- Given the challenges with VOCs as an underrepresented and incorrectly reported metric, sensitivity analyses should be conducted to test cost-effectiveness in populations with less stringent eligibility criteria (2 or more annual VOCs).

We recommend ICER incorporate these critical perspectives into the base-case and societal co-base analyses. If evidence is limited, ICER can work with Sick Cells to identify evidence sources or develop and administer surveys to gather necessary data.

Section 4: Comparative Clinical Effectiveness

- We thank ICER for utilizing this comprehensive list of patient-important outcomes in the scope of the review.
- Please define acute pain crises (VOCs) from the list of patient-important outcomes. Please describe any misalignment between the ICER definition of VOC outcome used modeling compared to the patient-important definition within the Uncertainty and Controversies sections.
- With many patient-important outcomes identified, please provide a decision framework for the selection of patient-important outcomes utilized.
- In Table 3.1 Overview of lovo-cel Clinical Study, please consider providing the median of the annualized incidence VOEs from the individuals with a baseline of four or more annualized VOEs in order to align with the scope of this review (i.e., individuals with severe SCD). ICER can use this median calculation to provide more accurate input for annualized VOCs in SOC economic modeling.
- The clinical trial sample sizes are very small. Generally, a sample size of at least 15 patients is recommended to have enough power to detect a clinically meaningful difference in response rates. Therefore, please clarify if these data from the lovo-cel unplanned interim analysis are used in the economic modeling, as ICER should view data cautiously. If ICER used unplanned interim analysis results, please indicate this limitation within the Uncertainty and Controversies sections.
- When discussing the lovo-cel trial results, please highlight the post-treatment annualized rates of severe VOEs for the one patient who continued to have acute pain episodes after treatment (0.5 severe VOCs).

Section 5: Long-Term Cost-Effectiveness

Methods Overview

- We recommend ICER explain the rationale for a model length of one year and include citations for prior published economic models/clinical data with this length.
- We recommend ICER include all acute and chronic conditions in the model, such as fever, splenic sequestration, priapism, dactylitis, acute anemia, clinical depression,

anxiety disorder, hearing loss, vision loss, and multi-organ failure. Please justify how ICER selected the nine acute and ten chronic conditions currently included. Please also correctly model chronic pain and fatigue to be separate complications.

- The report acknowledges that QOL affects patients and caregivers broadly; however, ICER's models in the report need to be clarified. ICER needs to explain how quality of life measures are incorporated into the model and how primary outcomes impact QOL within the model. Please also describe data sources and modeling effects for caregiver QOL impacts.
- Please update model estimate outcomes to include other patient-prioritized outcomes as primary efficacy measures (QOL, mental health, daily chronic pain, fatigue, and cognitive health).

Key Model Assumption and Inputs

- Please discuss the limitations of not utilizing patient-level characteristics that affect the efficacy of the intervention and SOC, such as the impact of co-morbidities or treatment adherence.
- Please clarify the population definition of severe SCD used in the base-case analysis.
- Please clarify each therapy used in SOC as the comparator, including frequency, dosage, unit costs, and any treatment adherence considerations.
- Please include the cycle length of the model in sensitivity analyses.
- Please update treatment effectiveness modeling only based on general population rates. It is an incorrect and harmful assumption to model based on people with SCD who experience no or limited VOCs.
- It is incorrect to assume that the small proportion of patients who experience severe VOCs after treatment will have the same rate of complications and mortality as those on standard care. Please update key model assumptions for estimating treatment failure and complication rates to align with clinical evidence:
    a. For the lovo-cel HGB 206 trial, only one patient experienced severe VOCs at a median annualized rate of 0.5, significantly below the SOC rate for annual VOCs.
    b. For exca-cel, all participants remained severe VOC-free.
- Clinical experts have expressed that the long-term durability of both products will be very high, and there is no reason to believe there will be a reduction in durability. It is highly inappropriate for ICER to use data from the beta thalassemia report to support model assumptions for the SCD report, given the different disease populations, treatments, and standards of care. Please update key model assumptions to a 0% revision and use sensitivity analyses to allow justification for the impact on costs.
- Please discuss limitations for populating the model with Medicaid patients from Mahesri et al. 2022, as patients without 12 months of continuous enrollment were excluded. This would likely mean that the model uses a lower prevalence of SCD than what is likely to be observed in Medicaid.
- Please justify using the additive approach for HRQoL, while other assumptions note that all complications are modeled independently. We recommend ICER use interaction terms or use multilevel modeling to account for the realities of impacts across

comorbidities.

- Please justify the assumption of organ damage accumulation for adults and the impact on hazard ratios. Please include specific age-dependent evidence to support the rationale and utilize sensitivity analysis to examine how hazard ratios vary based on the age of organ damage accumulation.
- We are concerned about the input used for the annual number of VOCs, as 4 VOCs seems to underestimate. We recommend that ICER use the input of 6 VOCs per year to align more with definitions, published evidence, and real-world experience. Additionally, individuals with three or fewer VOCs should be excluded from the economic evaluation based on the ICER's population definition of individuals with severe SCD.

Health Status Utilities

- ICER incorrectly assumes uncomplicated SCD (i.e., without any complications) to be 0.8 utility value; however, Anie et al. 2012 do not measure uncomplicated SCD. Within this UK-based study, patients reported a health utility score of 0.75 one week post discharge from a pain event. Evidence demonstrates that the impacts of pain events frequently last longer than seven days. Anie notes, "It was interesting to observe that patients were not completely pain-free on discharge and importantly at 1-week follow-up." We recommend that ICER identify additional sources of evidence to represent the experience of patients without pain or develop and administer surveys to address the data gap. Please discuss this limitation in the report and utilize sensitivity analyses to support assumptions around these inputs.
- It is unclear which citation ICER references for intervention-related disutility for Matza et al. 2020. Please correct this citation in the list of references. It is highly inappropriate for ICER to use data from the beta-thalassemia report to support model assumptions for the SCD report, given the different disease populations, treatments, and standards of care. Please clarify if Matza is based on the SCD or beta-thalassemia population. We recommend that ICER identify additional sources of evidence to measure intervention-related disutility or to develop and administer surveys to address these data gaps.
- Please discuss key model assumptions related to the resolution of acute and chronic complications for successful gene therapy. Please utilize sensitivity analyses for each assumption to support their use.
- Using a "halving" estimate to calculate treatment effectiveness on acute and chronic complications is inappropriate. We recommend ICER identify evidence sources or develop and administer surveys to address these data gaps.

Cost Inputs

- ICER used VOC cost from Shah et al. 2020. Shah (2020) did not use indirect costs and limited analysis to those with insurance coverage for more than 24 months of continuous coverage. We recommend ICER justify using VOC costs that lack these important considerations, as this results in underestimating the proportion of patient events and the average number of VOCs per patient.
- Please discuss the limitation of VOCs managed at home not captured in this analysis. ICER needs to justify how they calculate this cost input.
- Please provide cost inputs for patient-important costs such as transportation costs, impact

on educational achievement, and annual pain events treated outside the hospital system. Survey data from Sick Cells' work in the 2020 ICER review can be used as supporting evidence.

Societal Perspective Inputs

- The study by Graf et al. 2022 used a hypothetical scenario to estimate the economic benefits of a cure for SCD, which may not accurately reflect the real-world impact of a cure.
- The study conducted by Holdford et al. 2021 is an excellent study to estimate annual losses in unpaid costs. Still, Holdford did not account for the indirect economic burden on other family members or the community.

5. Results: Uncertainty and Controversies

- Several utility values and hazard ratios used in this report are cited from U.K. studies, such as Anie et al. 2012, Bailey et al. 2019, and Herquelot 2012. These measurements are inappropriate for this assessment, given the differences between health care, health care systems, and the impacts of race and ethnicity in the UK and the US. Complex historical and sociological processes influence the relationships between pain, hospital care, coping responses, and overall quality of life. We recommend ICER identify evidence sources or develop and administer surveys to address these data gaps.
- Please clarify the definition of the population of focus for the assessment. The report states, "The population of focus for the assessment is patients living with severe SCD, defined as having **an average of four** VOCs each year in the past two years." However, in other places in the report, ICER defines severe SCD as having four or greater VOCs requiring medical care each year.

5. Contextual Considerations and Potential Other Benefits

- We recommend ICER add another column to Tables 5.1 and 5.2 to explain (1) why the contextual consideration was not included in the model and (2) the additional data needed to include the contextual consideration in the model.

Table E5: Treatment Effectiveness on Acute Complication

- We noted inaccuracies in the Table for Treatment Effectiveness on Acute Complication that are not represented in the paper published by Baily et al. We recommend ICER review the table and make any necessary changes.

Sincerely,

Ashley Valentine, President of Sick Cells

Maggie Jalowsky, Director of Advocacy of Sick Cells