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May 15, 2023

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108

Re: Draft Evidence Report on Gene Therapies for Sickle Cell Disease

Dear Dr. Pearson:

The American Society of Hematology (ASH) appreciates the opportunity to provide comments to the Institute for Clinical and Economic Review (ICER) in response to the Institute's draft evidence report on *Gene Therapies for Sickle Cell Disease*.

ASH represents more than 18,000 clinicians and scientists worldwide committed to studying and treating blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sickle cell disease (SCD), thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients.

ASH has a longstanding commitment to combating inequities in healthcare and research. As part of this commitment, in 2015, ASH launched a transformative, multi-faceted, patient-centric initiative to improve outcomes for individuals living with SCD–a disease that illustrates critical health disparities and inequities. The ASH initiative supports advances in research, improving provider training and education, advocating for policies to expand access to care and improve data collection, as well as a consortium to advance Newborn Screening in Africa.

ASH appreciates the work that went into this analysis and the potential impact these gene therapies could have on the patients our members treat. Ultimately, ASH believes that individuals with SCD patients should have access to high quality, comprehensive care and the therapies that they decide are most appropriate in conjunction with their physician. The Society is pleased to take this opportunity to share feedback that we think is critical to the understanding of SCD and quality-adjusted life years (QALY) modeling and analysis outlined in this draft. ASH encourages ICER to consider the following comments and recommendations as the draft report is finalized and presented to the public as a recommendation on the cost effectiveness of the two gene therapies analyzed in the paper.

We will be addressing a number of topics, including:

1) Sickle Cell Disease background
2) Aspects of ICER's clinical benefit modeling
3) Importance of pain and suffering management
4) Considering other SCD therapies and interventions
5) Additional modeling considerations

Sickle Cell Disease Background

SCD is a rare disease primarily impacting African Americans and Hispanics. As noted, the field has suffered from years of underinvestment and people suffering from SCD have traditionally faced significant barriers to health care. In many cases, patients who arrive at an emergency room complaining of pain are turned away or are considered to be drug-seeking. The number of providers and specialists in SCD is low compared to the affected population. Adults often lack access to specialized, comprehensive care for SCD. The research investment in SCD compared to other rare diseases has been historically lacking, and as a result, there have not been many effective new treatments for SCD. These new gene therapies, should they be approved, represent a significant breakthrough for the SCD community.

The ICER draft report acknowledges a number of these unique challenges to the SCD community. However, ASH believes the draft report does not accurately reflect the inequities faced by this patient population and SCD-related challenges in the clinical development space in its cost effectiveness conclusions. ICER's modeling could be improved by acknowledging these patient challenges and other development challenges faced by sponsors.

Clinical Benefit Modeling

While this report and its calculations are focused on the impact on the population currently eligible for gene therapy, including older teenagers and adults, it is important for ICER to track and update the analysis over time as the research in children advances. We recognize that trials in children for gene-editing are ongoing, so it is premature to conclude anything about risk or benefit for this group at this time. It is also important to note that younger age is associated with improved overall and event free survival for allogeneic transplants for SCD, but data on children in the thalassemia gene therapy trials did not find that age mattered. Based on this information, early research, and findings that people would ideally benefit most from having gene therapy earlier in life, ASH encourages ICER to consider revisions to this analysis over time as gene therapy is approved for children.

The Society also encourages ICER to further investigate the extended benefits of additional effective sickle cell therapy. Treatment may reduce important health disparities that exist across racial and socio-economic groups in the U.S. People living with SCD are often on Medicaid and do not necessarily have access to the services they need for an appropriate standard of care regimen. SCD also pulls both patients and caregivers out of the workforce and educational setting. A previous ICER review relating to SCD notes that new therapies could reduce the caregiver burden, which would allow unpaid caregivers, for example, to potentially turn their focus to their own education, careers, and family. However, these therapies do not change the underlying socio-economic conditions of the affected population, so extrapolating lifetime earnings from a subpopulation with a higher rate of poverty is an inadequate analysis if factored into a cost per QALY.

That same review also noted that SCD treatments could decrease the disparity in life expectancy between Black and White Americans. Viewing these therapies through a health equity lens provides an important perspective on their value to the lives of Americans who have been historically underserved, and the large increase in QALY years demonstrates that these experimental therapies could profoundly transform many lives. We ask that ICER identify possible ways that its QALY analysis could incorporate this socio-historical qualitative perspective as it relates to potential new SCD therapies.

The management of acute and chronic pain for individuals living with SCD is a significant challenge throughout their lifespan. Pain causes significant morbidity for those living with SCD and has a serious impact on an individual's quality of life. Meaningfully reducing this suffering is a critical goal of treatments, and economic models that do not consider suffering are doing a disservice to the patient population whose

lives could be transformed by these therapies. The Society encourages ICER to better incorporate the patient perspective in its QALY analysis of these therapies. It is well known that the pain and suffering caused from SCD can be debilitating for a patient. This occurs not only in health care settings, but in the home, at work, and in the school setting. The economic toll of suffering from acute SCD is high, and therapies that improve or eliminate for some duration the pain and suffering should be valued against the economic costs that are caused by someone involuntarily removing themselves from the work force or requiring significant at home care in addition to professional care in a health care setting. The transaction versus transaction model employed by ICER does not capture this, and the QALY cost can be skewed higher as a result. We encourage ICER to identify and incorporate a pain management model into the broader work done by ICER on value-based pricing frameworks for products in the SCD space.

Another area ICER can improve its draft evidence report is relaying and incorporating patient important outcomes, which the SCD community has stressed to ICER in the past. For example, there is data demonstrating many SCD patients do not actually use emergency room (ER) services for every pain event, even those lasting for weeks at a time, due to past maltreatment at ERs or hospitals. Similar to the comments about pain mitigation, there are large societal and economic costs relating to pain events not treated in a hospital. Not only do these events keep patients out of school and work, but they also give a false impression of the true costs of the disease to the health care sector because they are not being treated in a health care setting. It is also important to consider the diminished ability for children who have strokes caused by SCD to succeed in school, which in turn has a lifetime impact on employment and earnings. Factoring these types of patient important outcomes into the statistical model would provide a more accurate account of the true costs of SCD both to the health system and to society. The cohort model employed in this study could also be reexamined, as a patient-level simulation might allow for more individual variability in the modeling given SCD is a complex disease that impacts the community differently.

Considering Other SCD Therapies and Interventions

We are pleased to see more therapies available for individuals with SCD; but as we have noted, current treatments and models of care do not adequately address the complex challenges of SCD. Additionally, many patients continue to experience access barriers with the existing therapies and interventions. It is important for this report to provide more detailed background on all therapies and interventions available for individuals with SCD, including the different types of potentially curative and non-curative options, with an emphasis on the need for patients to have access to whatever therapy is most appropriate for their case. This analysis could set the stage for future coverage policies, and it is important to have all interventions (and their benefit) clearly outlined in this report to avoid unintended consequences and prevent further access barriers and lead to denied access for patients.

ASH has spent years exploring ways to address challenges related to access to care for individuals with SCD and worked with policymakers to develop the Sickle Cell Disease Comprehensive Care Act to address these obstacles. This bill focuses on a demonstration program to improve access to high-quality outpatient care for individuals with SCD enrolled in Medicaid. The demonstration program includes the key elements of comprehensive (but low cost) management for SCD, which unfortunately is not available to most people with the disease in the United States. We encourage you to update the ICER analysis to not only include the current care delivery versus gene therapy, but to also incorporate the costs and benefits of making this type of comprehensive care available.

ASH recognizes that the SCD community has more treatment and curative options available today than in years past. These treatments provide options to people who, until very recently, had none. With the

variability of SCD within the community and the challenges associated with different treatment, we encourage ICER to view these gene therapies as additional (versus the only) treatment tools available.

ASH also encourages ICER to include hematopoietic stem cell transplantation (HSCT) as an alternative comparator, especially in the era of unrelated donor, mismatched, and haploidentical transplants, because survival after transplant is expected to be improved. ICER could even consider an analysis standardizing mortality rates with and without gene therapy, and with and without HSCT. The gene therapies being reviewed by ICER, should they receive U.S. Food and Drug Administration (FDA) approval, will be an important option for people living with SCD who may not be eligible for sibling donor match or worried about potential outcomes with other bone marrow transplants. Including HSCT as a comparator is important, but what is equally important is recognizing each person's unique experience with SCD and that simply having available options for treatment is extremely meaningful. Doctors and patients will decide what treatment option is best together, and it is clear that all of these treatment options provide better, more meaningful lives for a community that has been underserved for far too long.

Additional Modeling Considerations

ASH believes that an Outcomes Based Agreement (OBA) model for payment should be considered for the QALY modeling as it could yield more predictive results. With the Centers for Medicare & Medicaid Innovation's (CMMI) proposed Cell and Gene Therapy Access Model (CGT Access Model), state Medicaid programs can give the Centers of Medicare & Medicaid Services (CMS) the flexibility to create multistate OBA arrangements with manufacturers. Under these models, it is likely that some patients will receive a gene therapy treatment that does not work, in which case the payment model will account for this failure. These OBA's could lower the overall system cost of these therapies, which is not reflected in the current ICER model.

Comprehensive care pre-and-post therapy will be essential to the success of any treatment option. Wrap around services that provide specialist support as well as mental health, substance abuse, vision and dental care should be considered in a true definition of standard of care, but are far too often lacking for people with SCD and modeling reflects that. As ICER looks to refine its model for standard of care treatment as a comparator, we ask that it include the broad set of services that someone with SCD should have access to be fully supported for the disease and the host of complications it provides. This will also help address equity issues that arrive in the modeling, as we know people living with SCD do not tend to benefit from the basic standard of care, much less what should be the standard of care. Basing costs predominantly on Medicaid data does not truly capture the picture of the care someone with SCD should be receiving.

Additionally, costs relating to fertility preservation should be added to the baseline model for anyone undergoing a curative therapy, whether bone marrow transplant or gene therapy. Fertility preservation can be considered standard of care for adolescent and adult patients undergoing these treatments due to the myeloablative chemotherapy required to prepare a patient for transplant. The Society does not view these costs as connected specifically to gene therapies since anyone receiving certain medications for any indication will potentially require them. Instead, we view these as costs that should be incorporated into any standard of care model for current SCD treatments.

These gene therapies are not without risk. No SCD treatment is. From losing fertility function to potentially death, these treatments carry with them risks to the patient. The risks need to be strongly evaluated by the FDA when approving these therapies against the potential benefits they provide patients. The data presented with lovo-cel included four malignant events, including two deaths, and more research must be done on their causal elements though ASH notes that the gene therapy itself does not appear to be causal in two of

the malignant events. However, if these therapies are approved, the decision to seek them should be in the hands of medical professionals and their patients. Many treatments for many diseases carry risks but the treatment or curative potential can outweigh them. Bone marrow transplants often require myeloablative chemotherapy, which can cause malignancy on its own. For lifelong sufferers of SCD, we cannot model the cost/benefit analysis of any one individual's risk tolerance. However, as a medical community, we need to promote the research and development of improved therapies that build upon the success of current therapies with higher odds of a cure and lower odds of adverse events.

The long-term follow-up of individuals who undergo these treatments will be critical to ensure the best outcomes for those patients and to help inform the research and use of these therapies over time. It is imperative to have comprehensive data on these patients, toxicities, clinical management strategies, and a number of other important factors. The ICER report and modeling acknowledges the need for this type of ongoing, long-term monitoring, which will be quite costly to develop and maintain over time but is necessary for the patient and research community.

As you know and we have noted throughout this letter, SCD is a complex disease and there are so many factors and intricacies to consider before publishing this precedent setting report. These are developing therapies that are very exciting and range in cost from $200,000 to $3 million. Moving forward controlled trials comparing the different approaches and therapies will be necessary, especially as the technology evolves. Additionally, we think that it would be valuable for ICER to have additional engagement with the community and experts in the field to ensure that all perspectives and factors are considered and discussed. We request the opportunity to convene a meeting with the ICER review team and a panel of ASH SCD experts to expand on the items outlined in this letter as well as discuss additional items that are challenging to convey in writing.

ASH appreciates the opportunity to provide these comments. Please use ASH Deputy Director of Government Relations and Public Health Stephanie Kaplan (*skaplan@hematology.org* or 202-776-0544) as your point of contact to help facilitate the requested meeting and if you have any questions.

Sincerely,

Robert A. Brodsky, MD
President

The Black Women's Health Imperative's Response & Recommendations to ICER's Draft Evidence Report: Gene Therapies for Sickle Cell Disease

Submitted Electronically To: Kelsey Gosselin kgosselin@icer.org

Submitted By: Yoko Allen, MPH

May 9, 2023

The Black Women's Health Imperative (BWHI) is appreciative of the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report, ***Gene Therapies for Sickle Cell Disease*** and acknowledges ICER's aim "...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.[1] We at BWHI supports efforts that ensure an accessible, safe and highly efficacious treatment that will improve the quality of life of people living with sickle cell disease (SCD).

Established originally as the National Black Women's Health Project in 1983, the Black Women's Health Imperative is the first and only national non-profit organization formed for and by Black women dedicated to improving the health and wellness of our nation's 21 million Black women and girls -- physically, emotionally, and financially. Our core mission is advancing health equity, and reproductive and social justice for Black women across the lifespan through policy, advocacy, education, research, and leadership development.

Sickle Cell Disease from Africa to the United States

Originally from Africa and brought to the Americas by the forced immigration of slaves, sickle cell disease is diagnosed more frequently where the proportion of African descendants is greater. Carriers of the sickle cell trait have some resistance to the often-fatal disease, malaria. However, in the US, where only about 2,000 malaria cases are diagnosed each year, the trait no longer provides a survival advantage. Instead, it poses the threat of SCD, which occurs in children of carriers who inherit the sickle cell gene from both parents.[2,3]

Walter Clement Noel, native of Grenada, West Indies, was a dental student studying in Chicago when he complained of pain episodes and symptoms of anemia to cardiologist, Dr. James B. Herrick. Herrick assigned Noel's case to resident, Dr. Ernest Irons who examined Noel's blood and described his red blood cells as "having the shape of a sickle". When Herrick saw this in Noel's chart, he became interested in what might be a new, unknown, disease, and subsequently

published the November 1910 article, *Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia*, using the term "sickle shaped cells". [2,6]

Year 2023 marks the 113th year anniversary of sickle cell disease in the United States. Present in Africa for at least five thousand years and known by many names, the disorder "sickle cell disease" was discovered in the United States in 1910 and officially recognized by the US federal government in 1983.[2] More than 3.5 million Americans have sickle cell trait (SCT) and the prevalence of rates among African American is 9% (about 3 million people) and only 0.2% among Caucasians. [4,5]

Seeking An Accessible, Safe & Effective Cure

As noted in *ICER's Draft Evidence Report: Gene Therapies for Sickle Cell Disease*, standard of care in the most severe forms of SCD, usually involves hydroxyurea, as-needed blood transfusions, and supportive care for acute pain crises and other acute and chronic complications. Further acknowledged is that 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. Also, with the lack of compatible donors (especially those related to the patient), most people with SCD are unable to pursue HSCT as a therapeutic option even if there is interest.[1]

The Black Women's Health Imperative applauds ICER for acknowledging the current treatment with curative intent (HSCT) as presenting with high risk and limited access. ICER's Draft Evidence Report indicates that lovotibeglogene autotemcel and exagamglogene autotemcel may improve quality and length of life even with uncertainties about durability and harm.[1] Given the small sample sizes for both gene therapy clinical trials, the Black Women's Health Imperative recommends continued research with larger sample sizes for more reliable results that better represent the population.

Sickle Cell's Impact on Quality of Life & Experiences of NFL Players

The Black Women's Health Imperative applauds ICER for acknowledging adverse effects of limited treatment options, discrimination, stigma, inadequate pain management, disruption of family and social activities, and missed school and/or work on the SCD patients and caregivers – considering the disease's disproportionate impact on African Americans.[1]

In 1972, Congress passed the National Sickle Cell Anemia Control Act when an estimated 25,000 to 50,000 Black individuals were afflicted with the disease and an estimated 2 million Black Americans were carriers of the sickle cell trait. Many sickle cell anemia victims were crippled long before death, and some died, prematurely.[7] However, it wasn't until 2006 when all 50 states and Washington D.C. were mandated to screen all newborns for sickle cell disease.[8] After 113 years of its discovery in the US, sickle cell disease still vastly afflicts lives of African Americans.

Barriers to care and quality of life for people living with SCD are not foreign to even notable former and current NFL players like Santonio Holmes, Ty Montgomery, and Ryan Clark, who fought sickle cell during their playing careers, and shared their lived experiences during the cultural conversation series, *Playing with Sickle Cell*, hosted by the Black Women's Health Imperative. During the conversation series, Ryan Clark stated, "The overexertion caused my blood to sickle. It was difficult for medical professionals in sports to figure out what was wrong with me. It was a very uncommon thing." Despite his need for medical attention, Clark acknowledged that his symptoms are not as prevalent as many others and shared the experiences of his sister-in-law, who spent time in and out of hospitals before her death from sickle cell at the age of 27.

Ty Montgomery, a carrier of the sickle cell trait while playing in the NFL, did not know he carried the sickle cell trait until he was tested while a student-athlete at Stanford University, and, as a player at the professional level. Acknowledging the difficulty of being an athlete with SCT, Montgomery further noted that while growing up, he "cramped" a lot faster than everyone else and was hospitalized two or three times with "full-body cramps" no matter how much Pedialyte or water he drank. Being a high-risk player during the COVID-19 pandemic, he considered sitting out the 2020 NFL season, fearing that the onset of contracting the virus could negatively impact his career. "I was nervous that if I were to test positive, I could potentially have symptoms that would affect my career long-lasting," said Montgomery.

Former NFL player Santonio Holmes recalled finding out as an adult that he was a carrier of the trait and emphasized the lack of education and seriousness of the disease. "I found out that I had a lot of family members who had it, but no one ever spoke about it because it was like a 'foreign disease' that you don't want to have as a little kid. I can remember a young kid I went to school with, and his eyes would become yellow from having jaundice and we would look at him like there was something wrong with him, not knowing that I carry the sickle cell trait," said Holmes. He further expressed that people who lack awareness of its complications "make fun" of individuals living with the condition. Thus, to raise awareness and support families with sickle cell disease, Holmes formed the *III & Long Foundation* which provides financial support and treatment options.[9]

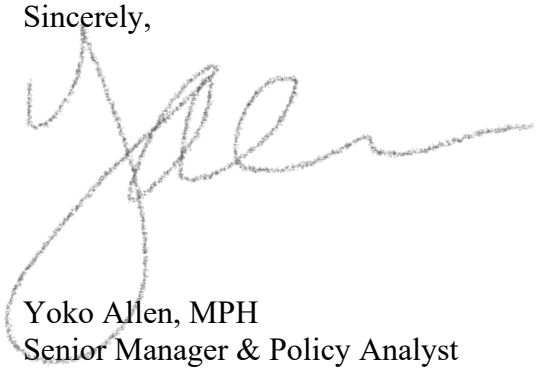
Countless stories like those shared by NFL celebrities may never reach a public platform, nevertheless social and financial support, outreach and education, screenings and access to quality care can improve the quality of life for people living with SCD.

The Black Women's Health Imperative recommends ICER's engagement with clinical and community stakeholders during the continuation of research/clinical trials for development of safe, effective curative treatments; comprehensive provider education for improving clinical impact and outcomes, and community outreach and education for understanding complications experienced by people living with sickle cell disease.

As affirmed by Linda Goler Blount, President and CEO of Black Women's Health Imperative, "The elite athletes are living proof that sickle cell is not undefeated. Black patients who show up, complaining about pain are not to be dismissed. They are to be treated, valued, respected and cared for so that they can live the life that we all want to live." [9]

Thank you for the opportunity to offer comments on *ICER's Draft Evidence Report: Gene Therapies for Sickle Cell Disease.* The Black Women's Health Imperative looks forward to ongoing engagement on this topic.

Sincerely,



Yoko Allen, MPH
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Black Women's Health Imperative

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9 May 2023

Emerging Gene Therapies for Sickle Cell Disease Review Team
Institute for Clinical and Economic Review (ICER)
14 Beacon Street, Suite 800, Boston, MA 02108

RE: bluebird bio's Response to ICER's draft report on Gene Therapies for Sickle Cell Disease

Dear ICER Review Team,

On behalf of bluebird bio, the manufacturer of lovotibeglogene autotemcel (lovo-cel), an investigational gene therapy for sickle cell disease (SCD), I thank ICER for its commitment to open dialogue throughout its evaluation of gene therapies for SCD and for the opportunity to provide input on the draft report. To begin, bluebird appreciates ICER's use of a modified societal perspective as the co-base case for this assessment in recognition of the substantial human and economic costs associated with SCD and aligned with the Single and Short-Term Transformative Therapies Methods Framework. We encourage ICER to anchor to this perspective when discussing the value of emerging therapies for SCD.

Below are several recommendations to further refine the draft assessment so that it best reflects current understanding of the disease, leverages the most appropriate available clinical evidence, and acknowledges the lived experience and priorities of individuals living with SCD. We look forward to advancing these ideas at the upcoming Public Meeting in July.

Recommendation 1: ICER should align to the available literature on SCD, as well as data from SCD gene therapy clinical studies, to appropriately assign the SCD morbidity and mortality risk for the proportion of individuals not achieving complete resolution (CR) of vaso occlusive crises (VOCs) (VOCcr).

ICER's current modeling approach assumes that patients who do not achieve complete resolution of VOCs following treatment with gene therapy will have the same rate of VOCs, complications, and mortality risk as patients treated with standard of care. This assumption is inconsistent with the considerable amount of literature characterizing the relationship between VOC reduction and risk of SCD-related morbidity and early death (Bailey M, 2019) (Shah N, 2019) (van Tuijn CF, 2010)—including the analysis that forms the basis for ICER's mortality risk assumptions in this assessment (Desai RJ, 2020). Additionally, by assigning an arbitrary threshold, this approach minimizes the significant impact that each VOC has on individuals living with SCD and their caregivers. Lastly, this approach is inconsistent with ICER's published methodology for Single and Short-Term Therapies, which seeks to evaluate emerging therapies of transformative benefit relative to standard of care.

To better inform ICER's draft recommendation, we are providing additional data from the HGB-206 study for the few individuals who achieved substantial reduction but not complete resolution of VOCs. (Please refer to Table 1 for these data, which are submitted to ICER as academic-in-confidence.) In short, all participants experienced sustained substantial improvements in anti-sickling hemoglobin that are expected to last a lifetime, substantial reductions in VOCs, and notable improvements in HRQoL. Additionally, SCD-related healthcare utilization for these individuals was dramatically reduced in line

with the Group C cohort response.

We appreciate ICER's re-evaluation of this assumption in light of these data, and request that ICER appropriately assign a differential risk for SCD morbidity and mortality for the proportion of individuals not achieving complete resolution of VOCs.

Recommendation 2: The model base-case should reflect a 0% durability loss, consistent with lentiviral vector (LVV) gene therapy mechanism of action and the latest available clinical data.

We disagree with ICER's assumption of loss of product durability, or a waning effect, introduced at year 7 of the economic model. The only opportunities to disrupt the anticipated lifelong expression of βA-T87Q are failure to engraft or spontaneous loss of graft; no patient within the HGB-206 Group C cohort has experienced either.

Gene therapy with lovo-cel consists of autologous transplantation of hematopoietic stem and progenitor cells transduced ex vivo with a lentiviral vector encoding a modified form of the βA-T87Q-globin gene. After infusion of lovo-cel, gene-modified hematopoietic stem cells are expected to undergo self-renewal and transfer a healthy copy of the βA-T87Q-globin gene to daughter blood cells for the lifetime of the patient. This mechanism of expression of the βA-T87Q-globin gene and production of HbAT87Q are expected to provide a lifetime of durable clinical benefits. In HGB-206, the ratio of HbAT87Q expression to HbS expression was stable within 1 year post lovo-cel infusion and has remained stable to latest follow-up of more than 5 years (Tisdale J, 2021). These data are further supported by other clinical studies of LVV gene therapy, including a program in transfusion-dependent beta-thalassemia in which stability persists to latest follow up beyond 8 years (Walters M, 2022), as well as testimony from leading clinical and scientific experts provided to ICER in the course of that review. Given the stability of relevant serologic markers of disease activity, the mechanism of action of lovo-cel, and the absence of engraftment failures, there is no scientifically rational argument to assign a durability loss after 7 years post lovo-cel.

Recommendation 3: ICER should use existing health state utility scores based on SCD gene therapy trial data to best reflect patients' experiences of the disease and the impact following therapy.

As ICER is aware, health state utility values are one of the few opportunities to directly incorporate the perspectives of patients into the economic model. Assigning an arbitrary value rather than utilizing available health state utility data from SCD gene therapy trials is a missed opportunity to appropriately account for the lived experience of patients. The EQ-5D-3L health state utility values from the HGB-206 study, as provided by bluebird, offer the closest understanding of the patient-reported impacts of disease and gene therapy treatment that is of interest in this review. We appreciate ICER's acknowledgement of the importance of community involvement in the HTA process and encourage ICER to prioritize inclusion of available patient-reported data whenever possible.

Additional Comments

Lastly, outside of these recommendations, we have several points for consideration to support our understanding of the draft report and increase transparency for public benefit. These additional points for consideration are:

- Regarding utility estimation, we ask that ICER provide greater transparency on the absolute values assigned to both arms of the economic analysis, including proportion of study participants assigned .85 on the gene therapy arm, as well as the distribution of other absolute utility values for the percentage of study participants with pre-existing and projected SCD-related morbidity. Additionally, the draft report refers to Supplemental Table E15 for disutility values, but this table is not provided.
- We appreciate if ICER can provide undiscounted results similar to Tables 4.6 and 4.7: *Results for the Base Case for lovo-cel and exa-cel Compared to Standard Care*.
- It would be beneficial to have Figure 4.2 (Tornado Diagram) updated with a one-way sensitivity analysis of the starting age of treatment that is 5-10 years younger, to account for the relevance of age-associated morbidity characterized in the report.
- Lastly, we appreciate ICER's attention to matters of accuracy that we have raised directly, including discussion of risk of hematologic malignancy related to conditioning regimens used for advanced therapies currently in development. We thank ICER for reflecting these changes in the revised and final reports.

In closing, we appreciate ICER's recognition of the significance of the potential availability of new therapies for SCD, and the importance of delivering an assessment that accurately reflects the value of these therapies to patients, the health system, and society, given the role this report may play in ensuring equitable access. Thank you for your consideration of the points above.

Sincerely,

Meghan Gallagher

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References

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Children's Hospital of Philadelphia
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3401 CIVIC CENTER BLVD.
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May 8th 2023

Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108

Dear ICER Colleagues,

We appreciate the opportunity to provide our feedback on ICER's assessment of cellular gene therapies for Sickle Cell Disease. We commend the organization's inclusion of clinical evidence, key-stakeholder input including patient perspective, and comparative clinical effectiveness research while accounting for value acquired from improvement in quality of life and overall potential for positive societal impact in this report.

The authors state that *"At least one patient treated with exa-cel has required ongoing phlebotomy to manage polycythemia."* We question where this information was derived from. However, not with any reference to any patient population, or any clinical trial, we can make the general observation that patients with thalassemia are iron overloaded. The most common treatment for iron overload after a successful transplant (of any kind) is phlebotomy. It is therefore possible that there could be a miscategorization of the need for phlebotomy as being related to polycythemia, which I (SG) have never heard of in a transplant setting, as opposed to iron overload, which we see frequently.

The authors state that "other adverse events such as infertility may require more than a decade to assess." Infertility is a *known and nearly universal* risk of blood and marrow transplant[1]. The strong potential for loss of fertility will be an important consideration for patients seeking curative cellular gene therapy treatment. Access to fertility preservation services prior to treatment will be critical to ensure equitable and timely access to novel cellular gene therapy treatments and the known risk and impact of infertility related to preparative regimens should not be underestimated.

The authors state that "Adverse events often occur more frequently when a therapy is used outside the careful monitoring of a clinical trial." We challenge this assumption. The first report of tisagenlecleucel in the real-world setting demonstrated outcomes with similar efficacy and *improved safety* compared with those seen in the pivotal trials[2]. While it is important to assess any change in risk-benefit after marketing, we do not expect to see an increase in adverse events in the post-market approval setting.

The authors state, "Gene therapy experts told us that long-term follow-up >15 years is required to establish precision around durability of the treatment effect." The FDA recommends

15 years of long-term follow up with the *primary goal* of detecting potential gene therapy-related delayed adverse events[3]. They, nor does any other regulatory body, explicitly state what constitutes adequate follow up to determine a given product's efficacy.

We appreciate your review of our comments and look forward to reviewing ICER's final assessment of gene therapies for Sickle Cell Disease.

Sincerely,

Claire White MSN, RN
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Cell Therapy and Transplant Section
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Stephan Grupp, MD PhD
Novotny Professor of Pediatrics
Co-Lead, Pediatric Program, Abramson Cancer Center
University of Pennsylvania Perelman School of Medicine
Section Chief, Cellular Therapy and Transplant, Division of Oncology
Director, Susan P. and Stephen S. Kelly Center for Cancer Immunotherapy
Medical Director, Cell and Gene Therapy Lab
Children's Hospital of Philadelphia

[1]CC Dvorak, CR Gracia, JE Sanders, et al. *NCI, NHLBI/PBMTC First International Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation: endocrine challenges—thyroid dysfunction*
growth impairment, bone health, & reproductive risks. Biol Blood Marrow Transplant, 17 (2011), pp. 1725-1738

[2] Pasquini MC, Hu ZH, Curran K, et al. *Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma*. Blood Adv. 2020;4(21):5414-5424. doi:10.1182/bloodadvances.2020003092.

[3] Food and Drug Administration. *Long Term Follow-Up After Administration of Human Gene Therapy Products: Guidance for Industry.* 2020

29April2023

Rafael Linares
1121 Harding Road
Elizabeth, NJ 07208

Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108
Re.: Public Comment for Draft Evidence Report on Gene Therapies for Sickle Cell Disease

Dear ICER,

For the Draft Evidence Report on Gene Therapies for Sickle Cell Disease, ICER had the number of patients with 12 months of follow-up 60 days post last RBC transfusion for Exa-Cel as 7 patients. CRSPR has released differing numbers of patients with 12 months of follow-up, as outlined below, from the few data sources I've found. Could ICER please provide clarification in the Final Evidence Report on the different numbers of patients with at least 12 months of follow-up reported in the various venues/timepoints?

November 15, 2022:

"All patients were VOC-free at the time of the data cut (duration of follow-up 2.0-32.3 months after exa-cel infusion; Figure). Median time from exa-cel infusion to last RBC transfusion was 19 (11-52) days. The mean proportion of HbF was >20% by Month 3, with mean total Hb levels >11 g/dL on and after Month 3. All 11 patients who have at least 12 months of follow-up after exa-cel infusion have maintained HbF levels >20% while experiencing no VOCs. At Month 6, the mean proportion of edited *BCL11A* alleles in bone marrow CD34+ HSPCs and peripheral blood mononuclear cells was 86.6% and 76.0%, respectively. These proportions remained stable in all patients who had ≥1 year of follow-up (Figure)."

https://ashpublications.org/blood/article/140/Supplement%201/29/490448/Efficacy-and-Safety-of-a-Single-Dose-of

February 21, 2023:

"All nine patients with greater than one year of follow-up as of the data cutoff date demonstrate a stable and durable response to treatment, including the first patient with SCD treated with exa-cel, who had a total hemoglobin level of 10.6 g/dL and HbF fraction of 41% at last visit, 30 months after exa-cel dosing."

http://ir.crisprtx.com/sec-filings?mobile=1&items_per_page=10&page=2

https://www.sec.gov/Archives/edgar/data/1674416/000095017023014870/ars_-_2022_ann_rep__swis.pdf

Published online **April 10, 2023:**

"All pts with SCD(n=31) no longer had severe VOCs after exa-cel infusion(duration 2.0 to 32.3 mo). The mean proportion of HbF was >20% by Month 3, increasing to ~40% at Month 4 and was stable thereafter, with mean total Hb levels >11 g/dL after Month 3.

Pts with TDT and SCD with ≥1 yr follow-up had stable proportions of edited *BCL11A* alleles in bone marrow CD34+ HSPCs and peripheral blood mononuclear cells."

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10112499/

ICER April 12, 2023:

"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]

39. Frangoul H, Locatelli F, Bhatia M, et al. Efficacy and Safety of a Single Dose of Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease. Paper presented at: 64th ASH: Annual Meeting and Exposition 2022.

Best Regards,

Rafael Linares

PIPC Partnership to Improve Patient Care

May 9, 2023

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) assessment of gene therapies for Sickle Cell Disease (SCD).

SCD is an incredibly challenging disease that disproportionately affects Black Americans. Following a historic lack of investment, in recent years some innovators have turned their attention to developing treatments and, now, gene therapies for SCD. PIPC followed and commented on ICER's 2020 assessment of treatments for SCD and have noticed ICER is still incorporating some of the flaws we and others pointed out in 2020, including continued use of the Quality-Adjusted Life Year (QALY), a failure to acknowledge that standard of care is often not standardized, and failure to adequately incorporate pain and other concerns like fatigue into its model.

PIPC encourages ICER to consider the following comments.

QALYs are an inappropriate metric for use.

PIPC has consistently urged ICER to abandon the use of the discriminatory QALY. Given the complex nature of SCD, its severity, and the fact that the burden falls onto specific groups within society, the QALY is a particularly inappropriate method for evaluating interventions aimed at its alleviation.[1] Numerous studies have highlighted that factors such as severity of disease,[2] pain levels, and sparse availability and limited effectiveness of alternative treatments should be considered key determinants of needing higher priority in healthcare settings.[3,4] A number of health technology assessment systems in Europe countries such as Norway, Sweden and the Netherlands[5] actively use information on these factors to inform approval decisions for new medicines, due to the limitations and simplicity of the QALY as a measure of health gain.

[1] Levenson JL, McClish DK, Dahman BA, Bovbjerg VE, Citero VD, Penberthy LT, Aisiku IP, Roberts JD, Roseff SD, Smith WR. Depression and anxiety in adults with sickle cell disease: the PiSCES project. Psychosomatic medicine. 2008 Feb 1;70(2):192-6.
[2] Nord E, Pinto JL, Richardson J, Menzel P, Ubel P. Incorporating societal concerns for fairness in numerical valuations of health programmes. Health Economics. 1999;8:25–39
[3] McKie J, Richardson J. Social preferences for prioritizing the treatment of severely ill patients: the relevance of severity, expected benefit, past health and lifetime health. Health Policy. 2017 Aug 1;121(8):913-22
[4] Gu Y, Lancsar E, Ghijben P, Butler JR, Donaldson C. Attributes and weights in health care priority setting: a systematic review of what counts and to what extent. Social Science & Medicine. 2015 Dec 1;146:41-52.
[5] Angelis A, Lange A, Kanavos P. Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. The European Journal of Health Economics. 2018 Jan 1;19(1):123-52.

ICER should prioritize the incorporation of heterogeneity of patients, both in terms of how they experience the disease, but also in terms of pure population group heterogeneity and the functional difference in access to and quality of the healthcare available to them. Ignoring this reality makes the results of the report difficult to interpret and potentially meaningless to guide what types of care should and shouldn't receive investment within the healthcare system.

When evaluating gene therapies or other "one-time" treatments that target chronic, progressive conditions, more care should be applied to capturing the benefit of limiting the burden of accessing regular care.

For patients with SCD, access to high-quality care can be challenging and for many patients out of reach. One of the potential value-adds of gene therapies is their use could ultimately reduce the burden on patients of poor health care access and delivery. Diseases that have the most limited current standard of care, or diseases where patients have suffered most from limited access to high quality care, is where the marginal value of gene therapies are likely to be highest. Whereas the ICER model expresses the marginal benefit between successful treatment of the disease with gene therapy and the optimum standard of care, which is unlikely to be experienced by the vast majority of SCD patients.

The ICER report itself states that patients commonly receive care from generalists, emergency nurses, and hospitalists who may not be equipped to help them manage their disease.[6,7] It also acknowledges that there are 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 revealed that only 20% of respondents felt comfortable treating SCD.[2,8] There is evidence of preventable 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. This is unlikely to have been the level of care represented in RCTs for the comparison arm, and so already marginal differences are underestimated. It would be more helpful to express a wider set of potential comparators than a 'standardized' alternate standard of care. While technically correct, the relative comparison described and reported by ICER is unlikely to be relevant to the majority of SCD patients. This approach not only ignores problems of access to standard treatments, but as a result underestimates the relative value of a one-off treatment for SCD, that bypasses the bulk of the limitations of the healthcare systems that SCD patients have been very clear about to ICER during both this assessment and its previous SCD assessment.

[6] Lee L, Smith-Whitley K, Banks S, Puckrein G. Reducing Health Care Disparities in Sickle Cell Disease: A Review. *Public Health Rep.* 2019;134(6):599-607
[7] Mainous AG, 3rd, Tanner RJ, Harle CA, Baker R, Shokar NK, Hulihan MM. Attitudes toward Management of Sickle Cell Disease and Its Complications: A National Survey of Academic Family Physicians. *Anemia.* 2015;2015:853835
[8] Begley S S. 'Every time it's a battle': In excruciating pain, sickle cell patients are shunted aside. https://www.statnews.com/2017/09/18/sickle-cell-pain-treatment/. Published 2017. Accessed 21 April 2023.

ICER's model underestimates incidence and costs associated with vaso-occlusive crises (VOCs)

The model uses Baldwin[9] as a source for the cost of VOCs. This paper is a systematic literature review. Within this review, the paper highlights marginal costs associated with a VOC, as ranging from $4,609 taken from Shah (2020a)[10] to $45,515, taken from Shah (2020b).[11] It is not clear why the ICER model just uses the number at the bottom of the range. It would be a more accurate representation to acknowledge the full range of potential costs associated with VOCs.

Similarly, the mean number of VOCs per year is listed as 4 with no source, as it is merely assumed. Assuming this value is concerning as it is one of the main drivers of cost-effectiveness in the model. In reality, the number of VOCs per year is highly variable, and, because of this, the potential value of successful treatment may vary considerably by severity of disease. The only systematic study collating all published research on the frequency of VOCs is Zaidi et al (2021),[12] which highlights this point. It concludes, from 52 studies, that although highly variable the proportion of patients experiencing ≥ 5 VOCs per year ranged from 18 to 59%. Despite this body of research, the range of VOCs presented in ICER's assessment is between 2 and 6, so it is likely that many patients are excluded from this sample.

ICER ignores the role of heterogeneity in severity of pain in estimating utilities, which is likely to underestimate the overall value of effective treatments in SCD.

Disease burden in SCD comes primarily from pain. Pain management has for many years been a primary part of disease management for SCD patients, and most SCD patients rank pain as being the most difficult part of having the disease.[13] It is also a large driver in differences in quality of life (and health utility) when determining the relative value of different treatments for SCD, but it has been largely ignored in the ICER model. SCD patients experience pain that is poorly understood and often poorly treated. Adult patients may face barriers to comprehensive SCD care and stigmatization of their care-seeking behavior by providers, forcing them into maladaptive coping strategies.[14]

A better attempt at addressing the role of pain in this exercise is necessary to fully comprehend the impact of its alleviation for sickle cell disease patients.

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[9] Baldwin Z, Jiao B, Basu A, Roth J, Bender MA, Elsisi Z, Johnson KM, Cousin E, Ramsey SD, Devine B. Medical and non-medical costs of sickle cell disease and treatments from a US perspective: a systematic review and landscape analysis. PharmacoEconomics-Open. 2022 Jul;6(4):469-81.

[10] Shah N, Bhor M, Xie L, Paulose J, Yuce H. Medical resource use and costs of treating sickle cell-related vaso-occlusive crisis episodes: a retrospective claims study. J Health Econ Outcomes Res. 2020;7(1):52–60

[11] Shah NR, Bhor M, Latremouille-Viau D, Kumar Sharma V, Puckrein GA, Gagnon-Sanschagrin P, et al. Vaso-occlusive crises and costs of sickle cell disease in patients with commercial, Medicaid, and Medicare insurance—the perspective of private and public payers. J Med Econ. 2020;23(11):1345–55

[12] Zaidi AU, Glaros AK, Lee S, Wang T, Bhojwani R, Morris E, Donohue B, Paulose J, Iorga ŞR, Nellesen D. A systematic literature review of frequency of vaso-occlusive crises in sickle cell disease. Orphanet Journal of Rare Diseases. 2021 Dec;16:1-2.

[13] McClish DK, Penberthy LT, Bovbjerg VE, Roberts JD, Aisiku IP, Levenson JL, Roseff SD, Smith WR. Health related quality of life in sickle cell patients: the PiSCES project. Health and quality of life outcomes. 2005 Dec;3(1):1-7.

[14] Smith, W.R., Bovbjerg, V.E., Penberthy, L.T., McClish, D.K., Levenson, J.L., Roberts, J.D., Gil, K., Roseff, S.D. and Aisiku, I.P., 2005. Understanding pain and improving management of sickle cell disease: the PiSCES study. *Journal of the National Medical association*, *97*(2), p.183.

Conclusion
PIPC urges ICER to reconsider the use of the QALY and ensure it is using accurate and representative inputs in its model.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

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

Tuesday, May 9th, 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). Our organizations represent the individuals most affected by your report - the patients and caregivers impacted by SCD and the community leaders who advocate for the SCD community.

Our comments will focus on key issues identified across the report and include recommendations to incorporate community perspectives into the revised report. The decisions you make in your report bear significant consequences — impacting coverage, access, out-of-pocket expenses, and many other outcomes. It is critically important for ICER to be thoughtful and deliberate in how it incorporates community input into the development of the economic modeling to ensure the analysis aligns with ICER's mission of amplifying the patient voice and supporting health equity in health technology assessments.

Our recommendations below center on the following key issues:

- Missing Data and the Premature Nature of the Review
- Urgent Need for Treatment Options
- Value and Efficacy Not Centered on Patient Experience and Perspective
- Incorrect Assumption of Annual VOCs
- Patient-Important Cost Not Included in the Base-Case Analysis
- Omission of Disease-Modifying Treatments in Costs and Definition of Standard Care

Missing Data and the Premature Nature of the Review

Racism has heavily affected the health care and outcomes of the SCD population since the clinical discovery of the disorder. For a century, the SCD community has been underfunded and devalued in research, innovation, and quality of care.[3] We would like to thank ICER for your work to listen to our patient community and appreciate how the "Background" section captures many realities of living with the disease.

Yet, your report does not account for the complexity of these issues and the larger implications they have on the rigor and accuracy of your cost-effectiveness conclusions. ICER has chosen to proceed with modeling and valuation despite known limitations in evidence and clear input from

concerned stakeholders about the equity implications of the premature nature of this review. Missing data is extremely problematic and will likely result in important unintended consequences. Given the concern that these other factors could easily confound your analyses, **we recommend ICER postpone this review until appropriate clinical evidence and real-world data are available.** If this is not possible, we expect ICER to provide justification and describe this within the "Uncertainty and Controversies" section in the final report.

Urgent Need for Treatment Options

Current treatments and models of care do not adequately address the complex challenges of SCD, which accounts for insurers paying $1.7 million on average for each person living with SCD.[4] These circumstances call for radical changes in the paradigm and practices of SCD care, including improving standards of clinician training, developing new research methods, and improving access and delivery of treatments. Because of its position in the U.S. health care field and its commitment to improve fair access across health insurance payer organizations, ICER is strategically positioned to make important contributions that will shape the future of SCD across the country. ICER's existing methods of cost-effectiveness analysis fail to adequately address this urgent need for treatments. **We recommend ICER incorporate these other potential benefits into the economic modeling used in this report.** If this is not possible, we expect ICER to provide justification and describe this limitation within the "Uncertainty and Controversies" section in the final report.

Value and Efficacy not Centered on Patient Experience and Perspective

Currently, there is wide variation in the definitions and metrics used as primary outcomes for SCD, and most notably, a misalignment between what is measured and what matters most to patients and their families. We applaud ICER for the inclusion of the list of patient-important outcomes, which highlights the patient-important short- and long-term outcomes and other related implications of SCD. However, modeling treatment effectiveness by using a primary measure of reduction in vaso-occlusive crisis (VOCs) perpetuates the aforementioned issue, as this is not centered on patient experience and perspective. Treatment success in the context of value assessment for gene therapy should be defined by the following patient-prioritized outcomes: improvement in health-related quality of life, improvement in emotional and mental health, reduction of the length and frequency of pain crises managed at home and medical setting, reduction in daily chronic pain, reduction in economic and financial burden, improvement in ability to age, reduction of fatigue, improvement in cognitive health and symptoms of mental fog, and reduction to the risk of organ damage and stroke. **We recommend ICER update the definition of treatment effectiveness and adjust the cost-effectiveness model to incorporate these patient-prioritized impacts as primary measures of efficacy.** If evidence is limited, ICER can work with patient groups to identify sources of evidence or to develop and administer surveys to get new data that can be used in the economic model. If this is

not possible, we expect ICER to include sensitivity analyses for each of these measures and describe this limitation within the "Uncertainty and Controversies" section in the final report.

Incorrect Assumption of Annual VOCs

There are noted differences between the definitions of severe SCD and vaso-occlusive crisis and events (VOCs and VOEs) used throughout this report, leading to confusion, inconsistencies, and incorrect assumptions. These differences are summarized below:

- In the lovo-cel trial, severe SCD was defined by **four or more severe vaso-occlusive events requiring health care** in the two years prior to enrollment.
- In the exa-cel trial, severe SCD was defined by **two or more severe VOCs requiring health care** per year in the two years prior to enrollment.
- The population for ICER's economic evaluation is stated as patients living with severe SCD. Severe SCD is defined as having **a minimum of four severe VOCs** in each of the two prior years.
- Later, in ICER's key model assumptions and inputs the patients on standard care were assumed to have **an average of four VOCs per year** until death. This creates a discrepancy compared to the population definition.

ICER's sensitivity analyses demonstrate that, for both treatments, the annual number of VOCs is a major driver of cost effectiveness, which raises concerns about ICER inappropriately choosing your assumption for the number of annual VOCs and undervaluing these treatments. **We recommend ICER update key assumption and inputs in base-case analysis to be more align with definitions, published evidence, and real-world experience**, by:

- **Correcting the input for the number of annual VOCs that require health care use to six VOCs per year.** The 2020 "My Life With Sickle Cell" survey collected information on VOCs from 454 patients and caregivers. Survey results indicate that individuals with SCD experience an average of 6.1 VOCs requiring health care use per year. This comprehensive study highlights the need to accurately reflect annual VOCs, which are typically under-represented in research.[5]
- **Removing non-severe patients or individuals with three or fewer VOCs per year from the average input criteria.** These individuals should be excluded from the economic evaluation based on ICER's population definition of severe SCD, which requires a minimum of four severe VOCs annually.

If additional evidence is needed, ICER should work with patient groups to identify sources of evidence related to the annual number of VOCs or to develop and administer surveys to get new data that can be used as a model input.

Patient-Important Cost Not Included in the Base-Case Analysis

Many patient-important outcomes and costs—transportation costs, impact on educational achievement, and annual pain events treated outside the hospital system[6], for example—are

omitted from ICER's analysis entirely despite strong and repeated emphasis on their importance from the SCD community during both the 2020 ICER review and the current review. For example, emerging data shows that patients often manage additional pain events at home each year that are typically excluded from calculated averages of annual VOCs. These events can last for days or weeks, with the main reason they chose to manage their VOCs at home due to previous poor experience in hospitals or Emergency Departments.[2,5,7] The exclusion of these outcomes from the model effectively assumes that the impact of these outcomes on value is equal to zero, which perpetuates issues like stigma and patients' experiences of racism and poor quality treatment during pain events. **We recommend ICER incorporate these patient-important outcomes and costs into both the base-case analysis and modified societal perspective analysis in order to accurately demonstrate the significance and burden of this disease.**

Omission of Disease-Modifying Treatments in Costs and Definition of Standard Care
Standard of care (SOC) for SCD is difficult to define, as different subtypes and individuals suffer from different complications, and comprehensive care is not clearly defined or standardized. ICER's definition of SOC raises concerns due to the exclusion of FDA-approved disease-modifying treatments. Several new treatments that have been approved over the last few years and are currently used in practice to manage severe SCD, including Adakveo®, Endari™, and Oxbryta®. Payer coverage policies often move coverage into concordance with standard of care defined in ICER reports, thus raising concerns that ICER's omission of these treatments will enable further access barriers and lead to denied access for patients. **We recommend ICER accurately reflect all available disease-modifying therapies in the definition of standard of care and estimate standard care costs based on the proportion of patients on each therapy, frequency, dosage, and unit costs for all FDA-approved therapies for SCD.**

We hope that you consider these recommendations. Should you have any questions or if you would like to discuss these comments further, please reach out to Sick Cells at info@sickcells.org.

Sincerely,

Advancing Sickle Cell Advocacy Project, Inc.
Association For Prevention of Sickle Cell Anemia Harford, Cecil, Eastern Shore
Axis Advocacy
Bridging the Gap - Adult Sickle Cell Disease Foundation of Nevada
Cayenne Wellness Center
Dreamsickle Kids Foundation, Inc.
Foundation for Sickle Cell Disease Research
Hope in Affliction, L.L.C

Kids Conquering Sickle Cell Disease Foundation
Martin Center Sickle Cell Initiative
May5Foundation
Metropolitan Seattle Sickle Cell Task Force
MTS Sickle Cell Foundation
North Alabama Sickle Cell Foundation, Inc.
Scott Center for Observation Treatment and Transition
SiCAWRE L.L.C.
Sick Cells
Sickle Cell Advocates of Rochester
Sickle Cell Association (St. Louis, MO)
Sickle Cell Association of Hillsborough County
Sickle Cell Association of Kentuckiana
Sickle Cell Association of Texas, Marc Thomas Foundation
Sickle Cell Association of West Alabama, Inc.
Sickle Cell Coalition of Maryland
Sickle Cell Community Consortium
Sickle Cell Disease Association of America, Central Alabama
Sickle Cell Disease Association of America, Inc.
Sickle Cell Disease Association of America, Inc. Northwest Louisiana Chapter
Sickle Cell Disease Association of America, Michigan Chapter
Sickle Cell Disease Association of America, Philadelphia/ Delaware Valley Chapter
Sickle Cell Disease Association of America, St. Petersburg Chapter
Sickle Cell Disease Association of Florida, Inc.
Sickle Cell Disease Association of Illinois
Sickle Cell Foundation of Minnesota
Sickle Cell Reproductive Health Education Directive
Sickle Cell Thalassemia Patients Network
Supporters of Families with Sickle Cell Disease, Inc.
The Maryland Sickle Cell Disease Association (MSCDA)
The Sickle Cell Association of New Jersey
The Sickle Cell Foundation of Tennessee
TOVA Community Health
Unspoken Hero Society
Uriel E. Owens Sickle Cell Disease Association of the Midwest
Virginia Sickle Cell Network
William E. Proudford Sickle Cell Fund Inc.
#ThroughThePain Inc.

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May 09, 2023

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Re: Vertex Pharmaceuticals public comments on the ICER draft evidence report concerning it's investigational therapy exagamglogene autotemcel (exa-cel)

Gene therapies for severe genetic diseases represent an important therapeutic advancement and hold the potential to cure once intractable diseases like sickle cell disease (SCD). We appreciate that ICER made a distinct effort to integrate the lived experiences of sickle cell warriors, their families, and caregivers in the report. While the overall model structure applied by ICER is appropriate to evaluate gene therapies for SCD, several model input decisions in the cost-effectiveness analysis systematically underestimate the burden of disease for sickle cell warriors who are experiencing recurrent vaso-occlusive crises (VOCs). As a direct consequence, the draft report underestimates the value of gene therapies for this disease. Below, we outline specific feedback on the draft evidence report.

ICER's choice to use the lowest available cost estimate for VOCs in the model underestimates the burden of disease associated with SCD, which as a direct result underestimates the value of gene therapies. ICER should update the VOC cost to reflect the more recent evidence utilized in their own prior SCD assessment.

The cost per VOC utilized in the cost-effectiveness model is based on the lowest cost number reported in a systematic literature review of SCD costs[1]. Specifically, the cost per VOC was based on a published study using the Medicaid analytic extract of individuals with SCD from 2009 – 2013[2], which is older than, and not consistent with, other available data. In ICER's previous assessment of non-curative therapies in SCD[3], ICER conducted a bespoke claims analysis to inform the cost of acute and chronic complications, including the cost of VOCs. In this current assessment of gene therapies, ICER uses many of the costs from their previous claims analysis to inform acute and chronic complications, except for the cost of a VOC. Moreover, ICER originally proposed using the VOC costs from their claims analysis (<18 years: $12,980, ≥18 years: $13,735) in the model analysis plan for this assessment, but instead chose to use a much lower cost estimate in the draft report ($5,335, inflated to 2022 US dollars).

ICER's choice to utilize an older and lower VOC cost, which is ~60% lower than ICER's own internal claims analysis and lower than any other cost reported in the systematic review [range: $5,335 – $13,944][1], substantially underestimates the economic burden of disease for people living with SCD and thus underestimates the value of gene therapies for these individuals. ICER should utilize a similar VOC cost as was used in their 2020 non-curative therapy assessment and inflate to 2022 US dollars to better reflect the true cost of these events.

ICER assumes that the impact of exa-cel on the risk of chronic complications and mortality for the adult population is limited to the reduction in VOCs. This undervalues the

transformative nature of exa-cel and does not account for other observed benefits from clinical studies that are known to impact the risks of complications and mortality, like increased total hemoglobin levels. ICER should update these rates/risks to better reflect the impact of gene therapies.

ICER assumes that adults living with SCD who have responded to a gene therapy have the same risk of mortality and chronic complications as people living with SCD who experience no VOCs. ICER's explanation that this assumption accounts for previous organ damage is not appropriate, as ICER already accounts for previous organ damage by assuming that a proportion of the modeled population have chronic complications at baseline. This likely would lead to double counting the impact of previous organ damage for people living with SCD in the model.

For pediatric individuals, ICER does apply some additional non-VOC treatment benefit. However, in ICER's previous evaluation of non-curative therapies in SCD, the treatment effect is not assumed to be different by age group[3]. Specifically, in its assessment of the clinical benefit of voxelotor, ICER acknowledged and assumed a hemoglobin-associated treatment benefit for both adult and adolescent individuals living with SCD. Additionally, ICER's assumption contradicts recently published literature that demonstrates the direct relationship between hemoglobin and end-organ damage in individuals with SCD in the US in a cohort of mostly adult individuals (mean age 37.9 years; 90.4% adult)[4]. This study found that the 1-year odds ratios for any end organ damage decreased monotonically with higher hemoglobin levels and that the 1-year odds were reduced by up to 83% for people with Hb ≥12 g/dL compared to people with Hb <7g/dL. A similar correlation between increased hemoglobin levels and reduced end organ damage was also seen in another recently published analysis of people living with SCD in the UK utilizing the Clinical Practice Research Datalink[6]. In clinical studies, treatment with exa-cel led to increased hemoglobin levels; 12 months after exa-cel infusion mean hemoglobin levels were 12.5 g/dL (n=9)[5]. These data strongly suggest that ICER is underestimating the impact of exa-cel on chronic complications by using rates/risks from a population of individuals living with SCD with zero VOCs and is not considering the hemoglobin data and known relationships between hemoglobin levels and organ complications. ICER should update these rates/risks to better reflect the impact of gene therapies.

ICER's assumption of treatment waning for exa-cel in the base case does not reflect the curative potential of exa-cel. Based on the mechanism of action (MOA) and clinical trial data to date, lifelong durability is expected.

Exa-cel is a gene edited hematopoietic stem cell (HSC)-based therapy and there is no known mechanism for HSC DNA to convert back to a wild-type sequence following CRISPR/Cas9 editing. A fundamental property of stem-cells is self-renewal, which is why modified DNA in stem cells will be propagated in perpetuity. Edits to hematopoietic stem and progenitor cells (HSPCs) are permanent and durable. In interim trial data presented on people living with SCD treated with exa-cel, at month six, the mean proportion of edited *BCL11A* alleles in bone marrow CD34+ HSPCs and peripheral blood mononuclear cells was 86.6% and 76.0% respectively and was stable in those with additional follow-up time[7]. All 31 people living with SCD were VOC-free after infusion (duration from 2.0 to 32.3 months from publicly available clinical trial data)[5]. Based on the MOA and clinical trial data to date, lifelong durability is supported.

Modified societal perspective is the best reflection of the value of gene therapies and all sensitivity analyses should be produced from this perspective. While ICER's modified

societal perspective attempts to capture the holistic impact of SCD, it fails to consider many important indirect impacts (i.e., out of pocket costs and caregiver disutility) in the economic evaluation of gene therapies.

ICER reports both the payer perspective and modified societal perspectives as "co-base-cases" in the draft evidence report. This is consistent with ICER's framework to produce the modified societal perspective when societal costs are large, and the impact of treatment is substantial. Considering the broad impacts of SCD on sickle cell warriors, caregivers, families and society, which are articulated in the "patient and caregiver perspectives" section of the draft evidence report, the modified societal perspective is more appropriate when assessing the value of gene therapies for SCD. All sensitivity analyses should be produced from the societal perspective.

In the modified societal perspective presented in this draft report, additional costs associated with lost productivity for people with SCD and annual losses in unpaid work for caregivers are included. While the modified societal perspective attempts to capture some of the indirect impacts of disease, ICER does not include additional elements of the modified societal perspective that were previously recognized in their assessment of non-curative therapies, including out of pocket costs and caregiver disutilities. These additional impacts should be considered in this assessment of gene therapies.

ICER's clinical evidence rating for exa-cel underestimates its clinical benefit and inappropriately suggests that exa-cel could be comparable to standard-of-care (SOC), despite the overwhelming clinical evidence otherwise.

ICER's rating of exa-cel clinical evidence as a C++ (comparable or better) inappropriately underestimates the clinical benefit of exa-cel compared to SOC. While ICER chose to focus only on those with at least 12-months of follow-up, it is important to note that currently, all 31 individuals who received exa-cel were VOC-free after infusion (duration from 2.0 to 32.3 months from publicly available clinical trial data). Data show that individuals with SCD experiencing recurrent VOCs (defined as having 2 or more VOCs for 2 consecutive years) are unlikely to spontaneously stop experiencing VOCs[8], confirming the overwhelming clinical benefit associated with exa-cel. People living with SCD treated with exa-cel also have clinically meaningful increases in fetal hemoglobin that occurred early and were sustained over time. Clinically, higher HbF levels have been shown to ameliorate symptoms such as vaso-occlusive crises (VOCs), leg ulcers, osteonecrosis, and acute chest syndrome (ACS)[9]. We plan to provide ICER with additional data with longer follow-up in the coming weeks and appreciate that timelines have been adjusted to ensure these data are considered in this review. ICER should also incorporate the fact that the exa-cel primary endpoint of severe VOC is more broadly inclusive than the lovo-cel severe vaso-occlusive events (VOE) criteria in ICER's clinical evidence rating for exa-cel.

While ICER consulted and incorporated the patient and caregiver community's perspectives in their report, the failure to incorporate health disparities into the cost-effectiveness model minimizes the significant health equity concerns for individuals living with SCD.

Sickle cell warriors often face barriers to care and consequently health disparities that are the result of longstanding systemic health inequities spanning racism, socioeconomic, and societal factors. Individuals living with SCD regularly face persistent inequities such as lack of appropriate access to quality health care regardless of geography and socio-economic status, as well as historic underinvestment in biomedical research. ICER should incorporate health equity into the economic

modelling, as noted in ICER's own recently published framework for "Advancing Health Technology Assessment Methods that Support Health Equity". Quantitative inclusion of health equity considerations could have a substantial impact on cost-effectiveness. Previously published modelling that utilized the distributional cost effectiveness analysis (DCEA) framework found that incorporating health equity (i.e., utilizing an equity weight of 2) in a model would value the quality-adjusted-life-year (QALY) gain associated with a curative therapy in people living with SCD at almost three times the amount of QALY gains in a non-SCD patient[10].

ICER should clarify statements regarding polycythemia in evidence report.

Safety is our top priority for patients and clinical trial participants. Throughout our CLIMB trials, participants have been routinely monitored for potential adverse events, including polycythemia. As of the date of this letter, no participants with sickle cell disease who received exa-cel have reported any polycythemia. Data on total hemoglobin levels in participants who received exa-cel show total hemoglobin levels below the upper limit of normal.

Lastly, as ICER considers feedback received and develops a final report, we encourage ICER to consult additional clinicians who have direct experience with both exa-cel and lovo-cel as expert reviewers.

Sincerely,

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Vertex Pharmaceuticals Incorporated

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