INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Gene Therapies for Sickle Cell Disease
Response to Public Comments on Draft Evidence Report

July 13, 2023

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Manufacturers		
bluebird bio		
1.	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.	ICER's Value Assessment Framework shares our approach for when we consider both the health care system and modified societal perspective as co-equal (co-base case). As this comment suggests, ICER deemed this assessment as one where the findings from both perspectives will be used in estimating ICER's Health Benefit Price Benchmark range. ICER remains committed to an opportunity cost perspective on determining appropriate cost-effectiveness thresholds for decision-making. Within this paradigm, academic work suggests a top threshold at approximately $104,000 per QALY based on direct health losses within the health system perspective. Adding more elements of value in shifting to the societal perspective suggests the need to lower the opportunity-cost threshold to below $104,000 per QALY when measuring further loss domains. Working from these insights, although we are not changing our effective threshold range for price benchmarks when referring to the modified societal perspective findings, ICER views the modified societal perspective findings with less certainty when translated using higher thresholds into value-based prices.
2.	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	We had a number of discussions with experts about this issue. The base case analysis includes several optimistic assumptions for patients successful on gene therapy (e.g., assuming the treatment effectiveness lasts the whole lifetime and additional utility bump associated with gene therapy beyond the utility gains due to reduced complications). As such, it was suggested that the small proportion of patients

	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.	(around 3.2%) in whom the gene therapy has failed could be assumed to be similar to those receiving standard care. An estimate of 100% treatment success was explored in an optimistic scenario, and the resulting incremental cost-effectiveness ratio was similar to the base case results (suggesting that this assumption is not a key driver of cost-effectiveness).
3.	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	We had a number of discussions with experts about this and heard that it would be possible for patients to revert if the population of infused stem cells that were not genetically modified became clonally dominant; it was felt that over a lifetime post-treatment, an estimate of 8% reversion was fair. An estimate of no reversion was explored in an optimistic scenario, and the resulting incremental cost-effectiveness ratio was very similar to the base case results (suggesting that this parameter is not a driver of cost-effectiveness).

	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.	
4.	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.	We appreciate bluebird's willingness to share data with ICER as academic in confidence. We had concerns about the methods used to generate the utility estimates from the HGB-206 study (e.g., small sample sizes, no control arm, and not sufficient evidence to support that baseline assessments were not influenced by prior acute events). Of note, some academic experts that we consulted suggested no evidence to support an additional utility increase beyond disutility values for acute and chronic event differences. Therefore, our approach is an evidence-based compromise within the bounds of plausible extremes.
5.	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 strive to be transparent and have offered to share the model via the model transparency program, which bluebird had opted out of participating. The disutilities are presented in Supplemental Table E8. We are modelling all the complications independently using an additive assumption for disutilities, rather than a typical Markov modelling approach. We have presented the breakdown on QALYs, including the QALYs lost due to acute and chronic complications, in the supplemental material.

6.	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*.	We have presented these results in the Supplemental material.
7.	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.	We have performed this as a scenario analysis and presented the results in the supplemental material.
8.	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.	We will make these changes.
Vertex Pharmaceuticals, Inc.		
1.	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.	We had a number of discussions with experts about the modelling. The base case analysis includes several optimistic assumptions for patients successful on gene therapy (e.g., assuming the treatment effectiveness lasts the whole lifetime and additional utility bump associated with gene therapy beyond the utility gains due to reduced complications), so we do not believe the draft report underestimates the value of gene therapies.
2.	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,	Expert input on the model analysis plan suggested the costs for VOCs were quite high. As such, we used estimates from Shah et al 2020 who report the average cost of VOCs for Medicaid patients across the different settings (i.e., inpatient, emergency room, outpatient, and office). We believe this estimate is appropriate as it reflects the cost of VOCs (rather than assuming that all VOCs are costed assuming an inpatient visit) for the population under consideration. Also, note that for the patients on standard care, the updated base case analysis assumes 5.1 VOCs per year (compared to four VOCs per year used in the draft report) for the whole lifetime. As such, we do not believe that the model

	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.	underestimates the burden of disease associated with SCD. We have also conducted one-way sensitivity analyses varying the costs of VOCs and the results are presented in the report (Figures 4.2 and 4.3).
3.	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.	In the absence of long-term data, we are attempting to make reasonable assumptions about morbidity and mortality. People with SCD who experience no VOCs likely have less organ/vascular damage at any given age than people experiencing multiple severe VOCs; this is not adequately captured in "chronic complications". Not all organ damage will heal in an adult even if SCD is "cured". We feel that our assumption of experiencing morbidity and mortality after gene therapy that is similar to someone who reached the same age with no VOCs is reasonable. Long-term data may show that this assumption is optimistic or pessimistic.
4.	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	We are changing "polycythemia" to "elevated hemoglobin" and have added further text to clarify the information that ICER received. Additionally, individuals who received therapeutic phlebotomy might have been recorded as having normal hemoglobin levels (after phlebotomy) and therapeutic phlebotomy does not appear to have been measured as part of the trials.

	exa-cel show total hemoglobin levels below the upper limit of normal.	
5.	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.	If Vertex has additional experts you would like us to speak with, we would be happy to consider it.

#	Comment	ICER Response
Clinical Experts		
American Society of Hematology		
1.	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.	Thank you for this comment. We highlight two recommendations from ICER's Health Equity white paper (pages 29-30): - "Avoid using quantitative equity-informative economic evaluation as a substitute for a deliberative process that should integrate multiple important social values in policy decisions." and - "If quantitative or deliberative approaches suggest higher priority be given to a treatment because of its potential to reduce health disparities, do not automatically translate that priority into endorsement of higher prices that will adversely affect patients." In other words, ICER's Value Assessment Framework relies on the deliberative process to integrate social values, including health equity, into judgements on the long-term value for money of interventions. ICER's process does not automatically increase the value-based price of interventions that have a potential to reduce health disparities given the potential for unintended consequences of higher prices in the current US health care ecosystem. If the US were to resolve health system inefficiencies such as access barriers for high value care and had standardized insurance for all Americans, then health equity weighted analyses (using evidence-based weights that remain understudied) would be more appropriate to consider in estimates of value-based prices.
2.	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	Thank you for this suggestion. Because manufacturers will be choosing a price at the time of launch, conducting research that supports value-based pricing before

	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 launch is critical. Given the uncertainties in the evidence and lack of long-term follow-up data, we encourage stakeholders to use ICER Analytics for future analyses using ICER's methods.
3.	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.	In the societal perspective, the model used median wage of US population to estimate the annual lost patient productivity, rather than using the data for a subpopulation. Similarly, the background survival used in the model was also based on the general US population.
4.	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.	We highlight that within ICER's draft report, we used US background mortality estimates that were age- and sex-adjusted, but were not adjusted for other factors such as race/ethnicity. Further, ICER's Value Assessment Framework relies on the deliberative process to integrate social values, including health equity, into judgements on the long-term value for money of interventions. ICER's process does not automatically increase the value-based price of interventions that have a potential to reduce health disparities given the potential for unintended consequences of higher prices in the current US health care ecosystem.
5.	The management of acute and chronic pain for individuals living with SCD is a significant challenge throughout their	We think we adequately captured this in the model through the quality of life (QoL)

	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.	impact of reduced acute complications such as VOCs (which are assumed to be eliminated after successful gene therapy) and the reduction in chronic complications such as pain and fatigue. We also include an additional utility bump for people who have been successfully treated with gene therapy beyond the utility gains due to reduced complications. Furthermore, the societal perspective analysis includes the impact of cure of SCD on patient productivity and caregiver costs.
6.	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.	We have specific places in our value framework for achieving life goals but costs of being out of school and work is captured in modified societal perspective, which includes the impact of cure of SCD on patient productivity and caregiver costs. We do not believe that a patient simulation modelling approach is better than our cohort modelling approach; given the scarcity of longer-term data in this population. Also, the aim of our analyses is to understand the cost-effectiveness at a population level (i.e., not for specific subgroups) and we believe that the current modelling approach is appropriate.
7.	We are pleased to see more therapies available for individuals with SCD; but as we have noted, current	This report is meant to focus on potential new curative therapies and is not a

	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.	discussion of all possible therapies. ICER previously reviewed other emerging therapies for SCD. We added additional language to further emphasize access.
8.	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.	We have added language about comprehensive care programs to the report. Additionally, if comprehensive care programs do reduce costs, then the price of gene therapy should be lower (due to reduced cost-offsets of standard of care).
9.	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.	ICER's expectation is that initially these therapies would only be used if HSCT isn't an option.

	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.	
10	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.	We offered both manufacturers a chance to provide information around their plans for pricing, including the use of an OBA and did not receive information suggesting that we should include an OBA within this assessment. From past experience, an OBA may reduce risk from the payer perspective, but would not change the deterministic expected value of a value-based price. Therefore, although we agree that risk may be reduced within an OBA, the derivation of a value-based price from the deterministic cost-effectiveness model remains unchanged.
11	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.	We are trying to model current state not what could be achieved in an improved health system. We applaud the work of ASH to advocate and improve care for SCD patients.
12	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	Clinical experts indicated that fertility preservation is not offered routinely and that when it is offered, it is not covered by health insurance. However, fertility preservation costs are included in the model.

	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.	
Children's Hospital of Philadelphia – Cellular Therapy & Transplant		
1.	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.	We did not misinterpret phlebotomy for iron overload. However, we are changing "polycythemia" to "elevated hemoglobin" and have added additional contextual details to the text.
2.	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. 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.	We have updated language around fertility in the revised report. Infertility, as with other adverse events, may require more time and real-world data to assess. The model includes cost of fertility treatment.
3.	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. 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.	We do not agree with this statement and a single example does not generalize to all post-market therapies.
4.	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. They, nor does any other regulatory body, explicitly state what constitutes adequate follow up to determine a given product's efficacy.	Thank you. ICER has no association with the FDA.
5.	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].	In the absence of long-term data, we are attempting to make reasonable assumptions about morbidity and mortality. People with SCD who

	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.	experience no VOCs likely have less organ/vascular damage at any given age than people experiencing multiple severe VOCs; this is not adequately captured in "chronic complications." Not all organ damage will heal in an adult even if SCD is "cured." We feel that our assumption of experiencing morbidity and mortality after gene therapy that is similar to someone who reached the same age with no VOCs is reasonable. Long-term data may show that this assumption is optimistic or pessimistic.
6.	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.	Gene therapy experts reported to ICER that waning of treatment effect was possible. Since <100% of HSPCs are modified, it is possible that clonal dominance of a an unmodified HSPC might occur even years after transplantation. Waning efficacy is a reflection of this and not an expectation of DNA converting back to wild-type. Long-term follow-up data are needed to further assess durability over time.
7.	Modified societal perspective is the best reflection of the value of gene therapies and all sensitivity analyses should	ICER's Value Assessment Framework shares our approach for when we consider

	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.	both the health care system and modified societal perspective as co-equal (co-base case). As this comment suggests, ICER deemed this assessment as one where the findings from both perspectives will be used in estimating ICER's Health Benefit Price Benchmark range. ICER remains committed to an opportunity cost perspective on determining appropriate cost-effectiveness thresholds for decision-making. Within this paradigm, academic work suggests a top threshold at approximately $104,000 per QALY based on direct health losses within the health system perspective. Adding more elements of value in shifting to the societal perspective suggests the need to lower the opportunity-cost threshold to below $104,000 per QALY when measuring further loss domains. Working from these insights, although we are not changing our effective threshold range for price benchmarks when referring to the modified societal perspective findings, ICER views the modified societal perspective findings with less certainty when translated using higher thresholds into value-based prices.
8.	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,	This is the first CRISPR therapy and there is still considerable uncertainty around this therapy in humans. ICER's rating of C++ captures the likelihood that exa-cel will have substantial net health benefit while also reflecting these uncertainties. The rating of C++ is more favorable than P/I.

	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.	
9.	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].	Thank you for this comment. We highlight two recommendations from ICER's Health Equity white paper (pages 29-30): - "Avoid using quantitative equity-informative economic evaluation as a substitute for a deliberative process that should integrate multiple important social values in policy decisions." and - "If quantitative or deliberative approaches suggest higher priority be given to a treatment because of its potential to reduce health disparities, do not automatically translate that priority into endorsement of higher prices that will adversely affect patients." In other words, ICER's Value Assessment Framework relies on the deliberative process to integrate social values, including health equity, into judgements on the long-term value for money of interventions. ICER's process does not automatically increase the value-based price of interventions that have a potential to reduce health disparities given the potential for unintended consequences of higher prices in the current US health care ecosystem. If the US were to resolve health system inefficiencies such as access barriers for high value care and had standardized insurance for all Americans, then health equity weighted analyses (using evidence-based weights that remain understudied) would be more appropriate to consider in estimates of value-based prices.

#	Comment	ICER Response
Patient/Patient Groups		
Black Women's Health Imperative		
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. 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.	Thank you for this input.
2.	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.	Thank you. We previously participated in the coreSCD project. There will be an opportunity to further explore and incorporate this comment in ICER's policy roundtable and policy recommendations that are part of the final report.
Sick Cells		
1.	<u>Section 2: Background</u> 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.	Thank you. We appreciated Sick Cells helping to recruit stakeholders to speak with ICER.
2.	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	In discussion with clinical experts, the noted treatments are not frequently used. Furthermore, the noted treatments do not have evidence suggesting that they are high value care. Therefore, to include them as standard of care in this report is not warranted.

	SOC.	
3.	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.	We expanded the text in the background section. Iron chelation is included as part of standard of care in our modeling.
4.	<u>Section 3: Patient and Caregiver Perspectives</u> 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 believes that if all parties would agree on using value-based pricing for pricing and coverage, much less time would be needed for these activities.
5.	ICER should include out-of-pocket expenditures and indirect costs such as childcare, transportation, and managing pain crises at home in the modeling.	We included some of these expenses in the modified societal perspective analysis, which includes the impact of cure of SCD on patient productivity and caregiver costs.
6.	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.	Thank you for this comment. The modified societal perspective is included as a co-equal analysis for this assessment.
7.	The impact of discrimination, stigma, and racial bias should be accounted for in the model through quantitative empirical measures.	Please see above comment.
8.	ICER should include a quantified description of when patients' health deteriorated so that potential benefits outweigh potential risks.	We are unsure what this concern is. If Sick Cells can clarify this, ICER may be able to address the issue in the Final Report.
9.	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).	Our use of these criteria is not meant to imply that individual decisions about therapy/coverage should be set by clinical trial requirements. We do include the annual number of VOCs as a parameter in the one-way sensitivity analyses and present the results in the report (Figures 4.2 and 4.3).
10.	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	Thank you for this offer to partner on a survey. We note, however, that not all evidence gaps can be addressed with a survey.

	gather necessary data.	
11.	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.	We recognize that there does not exist a universal definition of an acute pain crisis. Despite the variability in terminology, we have featured VOCs as a prominent patient-important outcome in our report due to stakeholder feedback. We outline the definitions of VOCs used in the pivotal trials of both therapies in Table 3.3 of the main report. The reduction in occurrence of severe VOCs used in the economic model is equivalent to that of the severe VOC outcome used in the lovo-cel pivotal trial.
12.	With many patient-important outcomes identified, please provide a decision framework for the selection of patient-important outcomes utilized.	Our selection of patient-important outcomes for this review were derived from a comprehensive literature search of the evidence as well as conversations and written feedback from a variety of stakeholders, including patients, clinical experts, and manufacturers.
13.	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.	Table 3.1 provides an overview of the HGB-206 trial of lovo-cel, with a description of the study design, population, and baseline characteristics. We reported all publicly available data for this trial. The updated base case analysis in the model uses 5.1 VOCs per year for patients on standard care based on data from Mahesri et al 2022, which presented the annual number of VOCs for patients with severe SCD.
14.	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.	We agree that the small sample size contributes to the uncertainty of the effects of the treatments. Explicit assumptions were made due to small sample size and this is discussed in the report.
15.	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).	The reduction in severe VOEs in trial HGB-206 are discussed on page 16 of our Evidence Report.

16.	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.	To clarify, the model length is 'lifetime' not one year. The model *cycle* length is one year, which is based on prior published economic models and the clinical data.
17.	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 model focused on key acute and chronic complications as well as risk of death. The complications selected were based on review of published literature, consultation with experts and discussion with manufacturers. We have included all acute and chronic complications that were suggested by manufacturers as those that should be considered for the modeling.
18.	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.	Health state disutility values were used to estimate QALY losses for acute and chronic complications. QALY decrements for acute complications were estimated considering the short duration of the disutilities. Chronic complications were assumed to last for lifetime (i.e., until death). An additive approach was used to estimate the QALYs to reflect modeling of the complications independently. More details about the disutilities are presented in Supplement E Table E8.
19.	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).	We think we adequately captured this in the model both through the quality of life (QoL) impact of reduced acute events complications such as VOCs (which are assumed to be eliminated after successful gene therapy) and the reduction in chronic complications such as pain and fatigue. We also included additional utility bump in for people who have been successfully treated with gene therapy beyond the utility gains due to reduced complications.
20.	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.	We do not believe that a patient simulation modelling approach is better than our cohort modelling approach; given the scarcity of longer term data in this population. Also, the aim of our analyses is to understand the cost-effectiveness at a population level (i.e., not for specific subgroups) and we believe

		that the current modelling approach is appropriate.
21.	Please clarify the population definition of severe SCD used in the base-case analysis.	There is no generally accepted classification of SCD severity; in the studies of the gene therapies under review, patients were required to have a minimum of four severe VOCs in each of the prior two years. The updated base case analysis in the model uses 5.1 VOCs per year for patients on standard care based on data from Mahesri et al 2022, which presented the annual number of VOCs for patients with severe SCD.
22.	Please clarify each therapy used in SOC as the comparator, including frequency, dosage, unit costs, and any treatment adherence considerations.	The costs of standard of care were estimated from Gallagher et al 2022, who present the five-year costs of severe SCD for Medicare, Medicaid, and commercially insured patients. We used the costs of outpatient pharmacy, outpatient other services, and outpatient visits for Medicaid patients as they are considered to be a reasonable estimate of standard of care costs (as they include the costs of hydroxyurea, chronic blood transfusions, and iron chelation therapies).
23.	Please include the cycle length of the model in sensitivity analyses.	The cycle length is not a model parameter that is varied in sensitivity analyses. As described in modelling good practice guidelines, the cycle length in the model is a choice made based on the disease under consideration, and we have selected a cycle length of one year based on prior published economic models and the clinical data.
24.	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.	There is no data regarding the long-term treatment effectiveness of these gene therapies. As such, we had to make assumptions and we had a number of discussions with experts about this issue. The base case analysis includes several optimistic assumptions for patients successful on gene therapy (e.g., assuming the treatment effectiveness lasts the whole lifetime and additional utility bump associated with gene therapy beyond the utility gains due to reduced complications). Given the absence of effectiveness data and the small number

		of patients in the clinical trials, we believe we our assumptions on benefit are reasonable.
25.	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: 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. For exca-cel, all participants remained severe VOC-free.	We had a number of discussions with experts about this issue. The base case analysis includes several optimistic assumptions for patients successful on gene therapy (e.g., assuming the treatment effectiveness lasts the whole lifetime and additional utility bump associated with gene therapy beyond the utility gains due to reduced complications). As such, it was suggested that the small proportion of patients (around 2.4%) in whom the gene therapy has failed could be assumed to be similar to those receiving standard care. An estimate of 100% treatment success was explored in an optimistic scenario, and the resulting incremental cost-effectiveness ratio was similar to the base case results (suggesting that this assumption is not a key driver of cost-effectiveness).
26.	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.	Gene therapy experts reported to ICER that waning of treatment effect was possible. Since <100% of HSPCs are modified, it is possible that clonal dominance of a an unmodified HSPC might occur even years after transplantation. Zero is as extreme as we could possibly be; this is ultimately an assumption that nothing goes wrong in 10, 20, 30 years. We think a patient-oriented group should hesitate to suggest to patients that there is zero chance of late failure of a therapy based on short-term data.
27.	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.	The cost-effectiveness results are for the severe SCD population and given most of the SCD patients are covered by Medicaid, the model was populated using data for Medicaid patients. It should be noted that only the risk of complications and death in the model were populated using data for Medicaid patients. The prevalence data used to estimate the potential budget impact is based on manufacturer data submissions and literature (De Martino et al. 2021).

28.	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.	Indeed, the disutilities used in our model were based on Sullivan et al, who used regression methods on a nationally representative dataset of 38,678 adults to estimate the marginal disutility of each condition, controlling for age, comorbidity, gender, race, ethnicity, income, and education. As such, we believe that the current additive modelling approach is appropriate.
29.	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.	In the absence of long-term data, we are attempting to make reasonable assumptions about morbidity and mortality. People with SCD who experience no VOCs likely have less organ/vascular damage at any given age than people experiencing multiple severe VOCs; this is not adequately captured in "chronic complications". Not all organ damage will heal in an adult even if SCD is "cured". We feel that our assumption of experiencing morbidity and mortality after gene therapy that is similar to someone who reached the same age with no VOCs is reasonable. Long-term data may show that this assumption is optimistic or pessimistic.
30.	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.	The updated base case analysis in the model uses 5.1 VOCs per year for patients on standard care based on data from Mahesri et al 2022, which presented the annual number of VOCs for patients with severe SCD.
31.	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	A recent systematic review by Jiao et al. 2022 was used to identify the sources that best reflect the utilities for US SCD patients eligible for gene therapy. As such, we believe the utilities used in the model are appropriate. Indeed, we have performed one-way sensitivity analyses varying the utility values and the results are presented in the report (Figures 4.2 and 4.3).

	gap. Please discuss this limitation in the report and utilize sensitivity analyses to support assumptions around these inputs.	
32.	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.	The intervention-related disutility relates to the reduction in quality of life due to the additional procedures required for gene therapy such as myeloablative conditioning for transplant. Given these issues are similar to that in beta-thalassemia, we believe the disutility used in the model is appropriate.
33.	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.	The hazard ratios for death, acute, and chronic complications are estimated as a hazard ratio estimated from published literature (for those with zero VOCs vs. those with 3+ VOCs) with a multiplier added on top to capture the additional benefit of gene therapy treatment. The hazard ratio multipliers are different for death, acute and chronic complications based on the age of treatment (i.e., adolescents or adults). In the base case, the hazard ratio multipliers for acute complications are 0.5 for both adults and adolescents while for death and chronic complications, the hazard ratio multipliers are 0.5 for adolescents and 1 for adults. We have performed extensive sensitivity and scenario analyses varying these assumptions. In the one-way sensitivity analysis, given the large number of complications, the hazard ratio multipliers are varied (rather than incorporating all the individual hazard ratio parameters for each of the nine acute complications, 10 chronic complications, and death) and the results are presented in Figures 4.2 and 4.3 of the report. We have also performed scenario analyses with optimistic and conservative assumptions regarding the benefit of treatment with lovo-cel or exa-cel were

		performed to reflect the uncertainty in the clinical data. In the base-case analysis, we chose to anchor successful gene therapy treatment effectiveness for acute, chronic, and mortality events to be between the general population rates and the patients with SCD who experience no VOCs. However, we have also performed scenario analyses assuming that the complication and mortality rates in the gene therapy arm are closer to the US general population rates (i.e., optimistic scenario). Alternatively, we also performed scenario analyses assuming that the complication and mortality rates in the gene therapy arm are similar to patients with severe SCD who experience no VOCs (i.e., pessimistic scenario).
34.	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.	There are no data on the long-term treatment effectiveness. Trials did not measure this because of the requirement of longer run follow up needed and as such, an assumption needs to be made in the modelling. Administering surveys will not address these data gaps. We believe the assumptions used in the base case analyses are appropriate, as we anchor successful gene therapy treatment effectiveness for acute, chronic, and mortality events to be between the general population rates and the patients with SCD who experience no VOCs. We have also performed scenario analyses with optimistic and conservative assumptions regarding the benefit of treatment with lovo-cel or exa-cel were performed to reflect the uncertainty in the clinical data.
35.	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.	We believe our unit costs for VOCs are appropriate as they are estimated from Shah et al 2020 who report the average cost of VOCs for Medicaid patients across the different settings (i.e., inpatient, emergency room, outpatient, and office). We believe this estimate is appropriate as it reflects the cost of VOCs (rather than assuming that all VOCs are costed

		assuming an inpatient visit) for the population under consideration. Also, note that for the patients on standard care, the updated base case analysis assumes 5.1 VOCs per year (compared to four VOCs per year used in the draft report) for the whole lifetime. As such, we do not believe that the model underestimates the burden of disease associated with SCD. We have also conducted one-way sensitivity analyses varying the costs of VOCs and the results are presented in the report (Figures 4.2 and 4.3).
36.	Please discuss the limitation of VOCs managed at home not captured in this analysis. ICER needs to justify how they calculate this cost input.	Note that for the patients on standard care, the updated base case analysis assumes 5.1 VOCs per year (compared to four VOCs per year used in the draft report) for the whole lifetime.
37.	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.	We used more recent publications to estimate the patient productivity and caregiver costs (Graf et al. 2022 and Holdford et al. 2021), which were suggested to us by the manufacturers, who recommended more recent publications as starting point for costs.
38.	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.	We feel it reflects most appropriate data for estimating the potential impacts of cure of SCD in the model.
39.	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.	Please see above.
40.	<u>5. Results: Uncertainty and Controversies</u> 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.	There are no data on the long-term treatment effectiveness. Trials did not measure this because of the requirement of longer run follow up needed and as such, an assumption needs to be made in the modelling. We believe the assumptions used in the base case analyses are appropriate.

41.	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.	There is no generally accepted classification of SCD severity; in the studies of the gene therapies under review, patients were required to have a minimum of four severe VOCs in each of the prior two years. The updated base case analysis in the model uses 5.1 VOCs per year for patients on standard care based on data from Mahesri et al 2022, which presented the annual number of VOCs for patients with severe SCD.
42.	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.	ICER's value assessment framework recognizes that not all aspects of value are best captured in an economic model. The elements here are explicitly not modeled as part of ICER's Value Assessment Framework process.
43.	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.	We do not see any need to make changes. We have checked and we did not find any inaccuracies.
Sick Cells – Community Sign-On Letter		
1.	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	We recognize that for newly approved treatments there are often limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents once approved for use. As such, we view comparative clinical effectiveness research, and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy. Even when there is uncertainty about the actual values used in the models, sensitivity analyses can highlight the range of plausible values and their impact on overall cost-effectiveness.

	describe this within the "Uncertainty and Controversies" section in the final report.	
2.	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.	We agree with the urgent need for treatment and that improving care is also imperative. We do not understand how this is related to a benefit to be incorporated separately in the model.
3.	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	There are no data on the long-term treatment effectiveness and a survey from patients would not solve this problem. Trials did not measure this because of the requirement of longer run follow up needed and as such, an assumption needs to be made in the modelling to make long-term extrapolations from current data. We believe the assumptions used in the base case analyses are appropriate. Our model includes relationships to many outcomes beyond the primary measure (VOCs) in trials. We believe our model is quite comprehensive as we include nine acute complications, ten chronic complications, and death. As such, we believe that our model does reflect patient experience and the key considerations for patients are all included in model.

	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.	We have also performed extensive sensitivity analyses and scenario analyses with optimistic and conservative assumptions regarding the benefit of treatment with lovo-cel or exa-cel were performed to reflect the uncertainty in the clinical data.
4.	• 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.	Thank you for this comment. There are indeed differences in the definition of SCD severity between the two trials. Furthermore, there are differences between eligibility in the trials and what was observed. In the draft report, patients on standard care were assumed to have four severe VOCs each year, which is more than that observed in the trials. The updated base case analysis in the model uses 5.1 VOCs per year for patients on standard care based on data from Mahesri et al 2022, which presented the annual number of VOCs for patients with severe SCD.
5.	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	Thank you for this comment. In the draft report, patients on standard care were assumed to have four severe VOCs each year, which is more than that observed in the trials. The updated base case analysis in the model uses 5.1 VOCs per year for patients on standard care based on data from Mahesri et al 2022, which presented the annual number of VOCs for patients with severe SCD.

	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.	
6.	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.	In the draft report, patients on standard care were assumed to have four severe VOCs each year, which is more than that observed in the trials. The updated base case analysis in the model uses 5.1 VOCs per year for patients on standard care based on data from Mahesri et al 2022, which presented the annual number of VOCs for patients with severe SCD.
7.	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	In discussion with clinical experts, the noted treatments are not frequently used. Furthermore, the noted treatments do not have evidence suggesting that they are

	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.	high value care. Therefore, to include them a definition of standard of care is not warranted.

#	Comment	ICER Response
Other stakeholders		
Rafael Linares		
1.	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?	Thank you for your inquiry. The CLIMB trial defined the primary endpoint as "the proportion of patients who have not experienced a severe VOC for at least 12 months after the infusion of exa-cel, starting 60 days after their last [red blood cell] RBC transfusion". Based on Figure 1 of the ASH abstract (Frangoul et al, November 15 2022), we calculated that 7 trial participants met this endpoint definition, specifically the minimum of 12 months of follow-up *starting 60 days from a patient's last RBC transfusion*. Other references to the number of patients with a minimum of 12 months of follow-up are measured at post-infusion of exa-cel (versus RBC transfusion) or are in the context of other study measures (e.g., hemoglobin levels).
Partnership to Improve Patient Care		
1.	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	We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. They are also only one component of the value

	inappropriate method for evaluating interventions aimed at its alleviation. Numerous studies have highlighted that factors such as severity of disease, pain levels, and sparse availability and limited effectiveness of alternative treatments should be considered key determinants of needing higher priority in healthcare settings. A number of health technology assessment systems in Europe countries such as Norway, Sweden and the Netherlands 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.	assessment. Specifically, many of the issues you raise are part of the Other Benefits and Contextual Considerations section, which are essential in assessing value.
2.	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.	ICER's goal is to discuss average benefits and average costs and unless there are specific populations that can be defined a priori, it is inappropriate to look at heterogeneous subgroups.
3.	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. 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. 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	We agree that gene therapy would potentially be less valuable if patients were routinely treated to the standard of care. We have further emphasized concerns over access to high-quality care.

	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.	
4.	ICER's model underestimates incidence and costs associated with vaso-occlusive crises (VOCs) The model uses Baldwin 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)[1] to $45,515, taken from Shah (2020b). 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.	Expert input on the model analysis plan suggested the costs for VOCs were quite high. As such, we used estimate from Shah et al 2020 who report the average cost of VOCs for Medicaid patients across the different settings (i.e., inpatient, emergency room, outpatient, and office). We believe this estimate is appropriate as it reflects the cost of VOCs (rather than assuming that all VOCs are costed assuming an inpatient visit) for the population under consideration. Also, note that for the patients on standard care, the updated base case analysis assumes 5.1 VOCs per year (compared to four VOCs per year used in the draft report) for the whole lifetime. As such, we do not believe that the model underestimates the burden of disease associated with SCD. We have also conducted one-way sensitivity analyses varying the costs of VOCs and the results are presented in the report (Figures 4.2 and 4.3).
5.	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	There is no generally accepted classification of SCD severity; in the studies of the gene therapies under review, patients were required to have a minimum of four severe VOCs in each of the prior two years. The updated base

	considerably by severity of disease. The only systematic study collating all published research on the frequency of VOCs is Zaidi et al (2021), 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.	case analysis in the model uses 5.1 VOCs per year for patients on standard care based on data from Mahesri et al 2022, which presented the annual number of VOCs for patients with severe SCD.
6.	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. 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. 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.	We think we adequately captured this in the model through the quality of life (QoL) impact. We include pain within both the acute and chronic complications that we believe the treatment is mitigating. We model the QoL impact of reduced acute complications such as VOCs (which are assumed to be eliminated after successful gene therapy) and the reduction in chronic complications such as pain and fatigue. We also include an additional utility bump for people who have been successfully treated with gene therapy beyond the utility gains due to reduced complications.