INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease
Response to Public Comments on Draft Evidence Report

March 12

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Response to Comments from Individual Patients, Caregivers, and the Patient Community

We are moved by the extraordinary number of public comments we received from individual patients, caregivers, and the community at large on our draft report on new therapies for sickle cell disease. We greatly appreciate the time and energy required to pause from the daily physical, emotional, and economic burden of battling sickle cell disease to provide us a glimpse into your experience. Patients described the appalling trade-off between choosing to manage intolerable pain from home or choosing to go to the emergency room, where many are met with racial prejudice, uninformed medical professionals, and a constant need to advocate for adequate pain management. We heard about the helplessness and guilt experienced by a child or a parent with sickle cell disease for the perceived burden imposed on or inability to care for the other. Parents commented on the great financial toll placed on a family in rotating in and out of a hospital and missing work, and the emotional toll of subjecting their child to the loneliness and isolation of long periods of hospitalization.

In living with this invisible chronic illness, some have surrendered any expectation for a normal life. And yet amidst being misunderstood and mistreated by all corners of our society and the health care system, we were amazed by your resilience as sickle cell warriors. Many of you have experienced relief from pain and anxiety, and reclaimed an active lifestyle after receiving blood transfusions, hydroxyurea or Endari. Others are in the process of trying the newly available therapies, and we hope that this new era of treatments will provide the relief and improve the outcomes most important to you.

We also heard from the community about concerns regarding the timing and limitations of our analysis. We recognize that for newly approved treatments, there is often limited data available. However, patients, clinicians and payers are already faced with decisions about clinical use, coverage, and price. Our goal is to help ensure that when new therapies become available, patients who would benefit from these therapies can actually access them. So in addition to reviewing the clinical and cost effectiveness of new therapies our review also explores many of the potential other benefits and contextual considerations surrounding these new treatments not captured in the clinical trials.

Your voice is critical to this process and we sincerely thank you for sharing your experiences and comments.

#	Comment	Response/Integration
Manufacturers		
Emmaus		
1.	ICER selects the least favorable rate ratio from FDA's exploratory sensitivity analyses as "Treatment Effect" for ICER economic calculations. This 0.91 rate ratio (calculated by dividing 3.9 by 4.3) selected by ICER from FDA's exploratory analysis is inappropriate and detrimentally underestimates the effect size (Figure 1).1 This is clear under "Model Inputs", "Treatment Effect", ICER report page 68 Table 5.12, where 0.91 is noted to be sourced from FDA's multiple imputations whereas other drug treatment effects in the table are calculated from published values (Table 1). This exploratory FDA ratio (0.91) is carried throughout ICER's economic calculations (Table 2 and Table 3). The FDA never concluded that L-glutamine's effect size should be based on the worst-case outcome from an exploratory analysis (0.91). Based on the 'Conclusions and Recommendations' section of the FDA Clinical Review, the effect size of L-glutamine is equal to the Hazard Ratio of 0.73 using a recurrent event analysis. This recurrent event analysis was FDA's answer to missing data, not the exploratory analyses that ICER presented, which used negative binomial regression (NBR) (Figure 2 and Table 4). In the 'Conclusions and Recommendations' section of the Clinical Review, FDA only specifically mentions the findings of the recurrent event analysis: (FDA: Endari Clinical Review, page 58) "FDA analyses considered alternative methods of handling incomplete crisis event counts that did not rely on imputation of incomplete counts and incorporated relevant study information such as the time spent on treatment before dropping out of the study. Particularly, a recurrent time-to-event analysis performed by FDA estimated sickle cell crisis rates per 48 weeks of 3 crises for patients treated with Endari vs. 3.8 crises for patients treated with placebo (HR: 0.73, 95% CI: [0.55, 0.99])." (emphasis added). Referring to Figure 1, three exploratory sensitivity analyses were carried out by the FDA. The Fully Conditional Specification (FCS) method is the most conservative method, yielding the worst possible rate ratio using NBR. The FCS approach involved multiple imputations adjusting for numerous variables that were and were not pre-specified: a) treatment group (Endari vs placebo), b) study site (5 regions), c) baseline hydroxyurea use, d) age, e) baseline crisis counts, and f) time spent on study to impute crisis counts for 24 patients that left the study early with crisis counts of "0" (Figure 1). The rate ratio (0.91) is not only used to account for acute crises in the ICER model (See ICER Draft Report Table 5.12), but also carries over into the calculation of other acute complications (Table 2); for example, in the derivation of "42.25" for acute pain crises, thereby diminishing L-glutamine effect over the lifetime by using this incorrect rate ratio. This must be corrected in ICER's Report. For crizanlizumab, ICER used the ratio of the annualized median as published NEJM article (1.63 divided by 2.98 = 0.547).2 For a more direct comparison, L-glutamine phase 3 study yielded annualized medians of 2.4 for L-glutamine and 4.3 for placebo which	***We originally used the 0.91 rate ratio because it came from an analysis that controlled for important potential confounders. After reviewing this comment and revisiting the FDA's medical review packet, we decided to update the model so that the results of the FDA's recurrent event analysis (HR 0.73, 95% CI 0.55, 0.99) are used in place of the 0.91 rate ratio from sensitivity analyses. As the recurrent event analysis formed the basis of the FDA reviewer's recommendation for approval of L-glutamine and did not rely on imputation, we agree that this estimate is a reasonable input to use in our model. We have also added a description of the recurrent event analysis results to the comparative clinical effectiveness chapter.***

	would yield a rate ratio of 0.558 (p=0.02; CMH with modified ridit).3 Action required: For consistency, ICER must use information contained within both the FDA package insert and Emmaus' NEJM-published (non-annualized) median difference of 3 divided by 4 = 0.75; or the Endari package insert recurrent-event time analysis intensity rate ratio = 0.75; or the recurrent event-time analysis as performed by the FDA reviewers hazard ratio = 0.73.	
2.	1.2 ICER omits key information ("exploratory analyses") from an FDA quoteICER presents partial quotes from the FDA Clinical Review that may incorrectly portray FDA's conclusion. ICER Draft Report, page 46, ICER writes: "The FDA conducted several sensitivity analyses using different assumptions about the dropout data. Their analyses suggested that the reduction in crises from L-glutamine versus placebo ranged from 0.4 to 0.9. Consequently, FDA concluded that the results show a 'modest trend supporting a claim of benefit for [L-glutamine]', but noted that in some analyses, the upper limits of the confidence intervals for rate ratios comparing the treatment groups included 1." (emphasis added).What the FDA actually said: (FDA: Endari Clinical Review, page 13) "In sensitivity analyses conducted by FDA, the reduction in crises over 48 weeks from L-glutamine treatment compared to placebo ranged from 0.4 to 0.9 crises. Together, these exploratory analyses can be interpreted as showing a modest trend supporting a claim of benefit for Endari." (emphasis added).ICER's statement implies FDA concluded that the results overall show a modest trend for benefit. In contrast, what FDA said was, "Together, these exploratory analyses can be interpreted as showing a modest trend supporting a claim of benefit for Endari."(emphasis added).1 The exploratory analyses that FDA conducted not only takes into account multiple additional imputation factors, but also were analyzed using negative binomial regression. This is a different statistical method than Cochran-Mantel-Haenszel, the test statistic used to analyze the primary endpoint. Action required: ICER needs to make it clear that the FDA is referring to exploratory analyses in the above statement.	***We have clarified the description of the FDA's conclusions. It now reads, "FDA concluded that the results of the sensitivity analyses show a 'modest trend supporting a claim of benefit for [L-glutamine]'…"***
3.	2.1 Emmaus disagrees with ICER regarding the safety of L-glutamine. ICER concludes: (ICER Draft Report, page 57) "However, with residual safety concerns and uncertainty about the clinical benefits due to trial limitations, we feel there remains a small risk that L-glutamine produces net harm overall, but that this risk is less than 10%." (emphasis added). ICER misinterpreted the dosing information from the REDOXS study and subsequently misconstrued concerns over increased mortality with L-glutamine use: (ICER Draft Report, page 49) "However, the safety data on L-glutamine from trials in other conditions provides less reassurance. The REDOXS trial of critically ill patients with multiorgan failure reported that patients treated with 0.35 g/kg/day of IV glutamine had significantly higher in-hospital mortality and mortality at 6 months than patients who did not receive L-glutamine." (emphasis added). The dose given in the REDOXS study was much higher than the recommended maximum dose of L-glutamine in sickle cell disease.6 The study also used different formulations of glutamine and also	***We have revised the description of the REDOXS study to clarify that the trial administered higher doses and different formulations of glutamine from what is indicated in the SCD population. Nevertheless, we remain uncertain about whether the benefit of L-glutamine outweighs the risk, given the trial limitations described in the report.***

	included the intravenous route of administration in critically ill patients with multiorgan failure, not sickle cell patients.6 Dipeptides (not L-glutamine) were administered as follows: 0.5 g/kg/day of IV alanyl-glutamine and 42.5g per day of both oral alanyl-glutamine and glycine-glutamine.6 This results in approximately 0.35 g/kg/day IV glutamine and 30 g/day of oral glutamine. For varying body weights, a table has been created to show that administration of these mixtures of dipeptides would have led to between 182% to 370% of total daily recommended dose of L-glutamine in SCD as shown in Table 5. Because of these factors, alongside the fact that these patients were not sickle cell patients but critically ill, multi-organ failure patients, FDA stated that, (FDA: Endari Clinical Review, page 103) "Two other studies of interest (Heyland, Muscedere et al. 2013, van Zanten, Sztark et al. 2014) […] reported an increase in mortality among critically ill patients who received parenteral nutrition containing glutamine. These studies were conducted in critically ill, mechanically ventilated patients with severe sepsis and multi-organ failures, and included both intravenous and enteral supplementation. The findings from these studies are therefore not applicable to the patient population for whom Endari use is being sought in this application." (emphasis added). Action required: ICER has incorrectly referenced a study, consequently misconstruing the safety profile of L-glutamine in sickle cell disease at the prescribed dose level. Based on these reasons, ICER's conclusion that there is a risk that L-glutamine produces net harm overall should be withdrawn.	
4.	3.1 In ICER's assessment of the L-glutamine Phase 2 clinical trial: (ICER Draft Report, page 30) "We considered the Phase II trial of L-glutamine to be poor quality because of differences in the groups assembled at baseline, a large and differential rate of drop-out, and inadequate control for potential confounders (e.g., hydroxyurea use)." (emphasis added). The Phase 2 clinical trial was a proof of concept study and study data were integrated with the phase 3 data only for FDA safety analyses, not for efficacy.	***We maintain that the Phase 2 clinical trial of L-glutamine was poor quality using criteria developed by the United States Preventive Services Task Force to rate the quality of individual RCTs and cohort studies. These criteria are described in Appendix D of ICER's report. Nevertheless, we have now specified that the Phase 2 trial was a "proof of concept" study in the report's description of Key Studies of L-Glutamine.***
5.	ICER's assessment of the L-glutamine Phase 3 clinical trial: (ICER Draft Report, page 30) "We rated the Phase III trial of L-glutamine to be fair quality because there was a high and different loss to follow-up between groups; statistical imputation to account for these differences may have introduced further bias." ICER refers to discontinuations and imputations: (ICER Draft Report, page 46) "Due to the high and differential rate of trial discontinuation prior to the completion of the 48-week treatment period, investigators in the Phase III study imputed the crisis results […] This method may have introduced bias in the results because the high number of non-completers meant that the large proportion of imputed counts may have changed the distribution of data." At first glance, there may appear to be bias in favor of glutamine by using the protocol pre-specified imputation method (ICER Draft Report page 46) where patients were imputed with a value of 3 crises for the glutamine arm and 4 crises for the placebo arm. Because of the differential dropout rate (glutamine > placebo by 12%) more imputations were made in the L-glutamine arm where patients exited the study with 0, 1, and 2 crises than those in the placebo arm. More	***We remain concerned about the potential for bias in the primary efficacy analysis given its sensitivity to the imputation approach taken. We are unable to comment about the "additional analysis" referred to in this comment without further details about how these numbers were derived.***

	crises were added to the glutamine arm (106) than the placebo arm (34).3 Keeping in mind the 2:1 randomization, this evaluation showed that the imputation method as pre-specified in the protocol did not bias the results in favor of L-glutamine (Table 6). An additional analysis was performed taking into consideration time on study using the pre-specified imputation method and found that 3.37 and 3.40 events per patient-year were added to non-completers in the L-glutamine and placebo groups, respectively.3 This evaluation supports the fact that the imputation method pre-specified in the protocol did not bias the results in favor of L-glutamine.	
6.	ICER criticizes the L-glutamine study for high discontinuations While ICER criticizes the "large rate of trial discontinuation" in the L-glutamine study (throughout their document), ICER omitted mention of dropout rates in other sickle cell trials, in particular, the SUSTAIN trial. The Phase III study of L-glutamine overall dropout rate was 32% while the discontinuation rate in the SUSTAIN trial was 35%.2,4 ICER also refers to imputations for missing values only for the L-glutamine study ICER omitted mention of imputations being made when calculating "annualized medians" as performed in the crizanlizumab study. From the crizanlizumab NEJM publication itself: "The crisis rate for every patient was annualized to 12 months. The annual crisis rate was imputed for patients who did not complete the trial." (emphasis added).2 Using an annualized imputation method, one cannot impute for zero counts at early discontinuation Referring to the SUSTAIN trial, ICER states "At the end of the treatment phase, 36% of the crizanlizumab group had a crisis rate of zero, compared to 18% of the placebo group." (ICER Draft Report, page 33). In comparison, the L-glutamine phase 3 study had 23% (35/152 patients) in the treatment arm with a crisis rate of zero as compared to 10% (8/78 patients) in the placebo arm.3 Action required: ICER should remain consistent across studies in sickle cell disease when referring to high discontinuation rates and raising the issue of uncertainty in study endpoints due to imputations. We request ICER to refrain from overly criticizing the dropout rate and subsequent imputations in the phase 3 trial of L-glutamine.	***Dropout rates were presented for all key trials, and are always concerning when high, but were not emphasized for the trials of crizanlizumab or voxelotor because rates were comparable between intervention arms. We were particularly concerned about the differential rate of discontinuation in the L-glutamine studies with higher rates of discontinuation in patients receiving the active therapy in the Phase 3 trial.*** ***The primary efficacy analysis in the crizanlizumab study accounted for early dropouts by annualizing the rate of crises; patients who died were imputed the maximum event rates among all patients. This method did not concern us as much as the method applied in the Niihara 2018 study.*** ***We are comfortable presenting the proportion of patients with a crisis rate of zero for crizanlizumab given the consistency in results between the intention to treat and per protocol analyses.***
7.	4.1 After reading the FDA clinical review of L-glutamine, ICER expressed concerns for publication bias regarding L-glutamine: (ICER Draft Report, page 45) "Two additional Phase II studies were identified in our review of the FDA clinical review packet for L-glutamine and the clinicaltrials.gov site that would have matched our PICOTS criteria for inclusion. Both trials seemed to have been completed more than two years ago, yet our literature search did not find any publications related to these trials. We have summarized the limited information we have for these two studies in Appendix Table D18, but note that there may be potential publication bias in the evidence supporting L-glutamine." Emmaus understands ICER's concern related to the lack of public disclosure of data related to the two studies listed in Table 7. Study 8775, noted in ICER Table D18, was an early proof-of-concept conducted to evaluate the frequency of	***Thank you for clarifying. We have corrected the typographical error and revised the statement about potential publication bias.***

	sickle cell crises, number of hospitalization days, number of painless days on study, and safety. This study enrolled patients between December 1998 and January 2003. Since only 6 out of 24 patients completed the trial, there was insufficient data for primary endpoint analysis. Nevertheless, the study was presented as an abstract by Koh et al., at the Sickle Cell Disease Association of America meeting in Covington, Kentucky and the 28th National Sickle Cell Disease Program in April 2005. Note: There is an apparent typographical error in the "Results" column of the ICER Table D18 where "there was a significant increase in the number of pain days…" should read "there was a significant increase in the number of painless days". From the FDA Clinical Review, page 35, "In the 6 evaluable subjects, there was a significant increase in the number of painless days (p = 0.00885)." This is pointed out to ICER in order to alleviate any concerns by readers that this study was unpublished because of a negative finding (such as increased pain-days). Study 10511, noted in ICER Table D18, was an early proof-of-concept that studied the effect of L-glutamine on exercise tolerance in sickle cell patients. This study enrolled 15 subjects between February 2004 and August 2008. The key efficacy parameters describing exercise endurance were peak work rate (watts) and endurance (minutes). The exercise test was performed at baseline and at Week 10. This study was not published because it did not reach the targeted enrollment of 50 subjects and the decision was made to terminate the study. Actions required: 1) ICER to correct language in their table D18 to change "pain days" to "painless days". 2) ICER to remove "but note that there may be potential publication bias in the evidence supporting L-glutamine." from their draft report.	
8.	Transfusion is a mainstay in the management of sickle cell disease (SCD) patients and should be considered "optimal usual care". Transfusion modalities, including simple transfusion, manual transfusion and automated red blood cell exchange are different procedures as noted in the recently published American Society of Hematology (ASH) guidelines for transfusion support.1,2 As such, each transfusion modality has a unique procedure, required equipment, clinical consideration as an intervention for the treatment of sickle cell disease and its related complications and treatment costs. Patient risk and benefits also differ between the three different transfusion modalities, as described below.	***For the purposes of this report we used the same definition for the "comparator" as was used for the placebo groups in the clinical trials. We chose to use the term "Optimal Usual Care" because we heard from both patients and physicians that the care patients received in the placebo arms of these studies was much better than patients usually receive in the real world.***
Global Blood Therapeutics		
1.	GBT appreciates the opportunity to comment on ICER's Draft Evidence Report for crizanlizumab, voxelotor, and l-glutamine for Sickle Cell Disease (SCD). SCD is a unique disease that affects a historically overlooked, underserved, and underrepresented population. With limited investment, only a few treatment options were available for SCD before 2019, a challenge compounded further by the inadequate access SCD patients have to quality health care services. The annual cost of medical care in the U.S. for people who suffer from sickle cell disease exceeds $1.1 billion. Moreover, care for SCD patients with complications can cost the healthcare system more than $250 thousand dollars per patient per year, a cost that can be offset by novel disease modifying treatments, which also improve patient outcomes and quality of life. OxbrytaÔ (voxelotor) was approved by the FDA under accelerated approval due to limited treatments options and the urgent need to address the symptoms, morbidity, and	***We recognize that for newly approved treatments there is 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.***

	mortality in SCD that are not attended to by optimal usual care (OUC). As a result of these challenges, including the nascent stage of investment in SCD treatments relative to other diseases, we believe it is wholly unnecessary for ICER to conduct a value assessment of novel SCD treatments. Patients are more likely to be harmed than helped by ICER's assessment which inaccurately characterizes the potential value of novel therapies.	
2.	While GBT does not believe ICER's assessment of SCD therapies is appropriate, our substantive concerns about ICER's draft evidence report can be summarized in two points: 1) Voxelotor's evidence rating should be higher considering the totality of the evidence around voxelotor's efficacy and the role of Hb as the most important independent predictor for end organ damage (EOD) and survival in SCD; and 2) Voxelotor offers good value for patients and the SCD community, if assessed with the appropriate value framework and model parameters (See Figure 1 next sheet).	***See response to GBT row 3 and 8.***
3.	Voxelotor's evidence rating should be higher considering the totality of the evidence around voxelotor's efficacy and the role of Hb as the most important independent predictor for end organ damage and survival in SCD. Hb is the most important indicator in predicting risk of end organ damage in SCD and survival. Specifically, deoxygenated HbS polymerization is central to the cause of SCD (as it drives the molecular pathogenesis). Thus, by inhibiting HbS polymerization in red blood cells, increasing Hb and reducing hemolysis, voxelotor has the potential to modify outcomes in SCD, which should be reflected in ICER's evidence report. Equally, HbS polymerization is extraordinarily sensitive to deoxygenated HbS concentration, such that even tiny modifications in concentration result in sizable effects on polymerization. ,	***ICER considered the totality of evidence for voxelotor when assigning an evidence rating. As noted in Chapter 4, Summary and Comment, there is not yet evidence available to demonstrate that the improvement in a surrogate endpoint (increase in hemoglobin) translates into improvements in clinical outcomes that are meaningful to patients. We therefore maintain that the evidence for voxelotor is "promising but inconclusive."***
4.	Any clinical or value assessment of voxelotor should reflect the current regulatory understanding of the role of Hb in SCD. The importance of both Hb and inhibiting HbS polymerization in the treatment of SCD was recognized by the Food and Drug Administration (FDA) in granting accelerated approval of voxelotor. The U.S. Congress and the FDA established the accelerated approval pathway for drugs that treat serious conditions, fill an unmet medical need, and are approved based on evidence which is reasonably likely to translate into patient benefit. This balanced approval construct supports an important public policy interest by ensuring patients' timely access to medicines that are safe and highly likely to produce clinical benefit, while the sponsor conducts additional, confirmatory clinical trials as agreed by the FDA. Appropriately quantify voxelotor's impact on quality of life. ICER's model does not give voxelotor any HRQoL benefit based on the results: this is not clinically accurate and challenges the model's underlying validity. In ICER's model, the optimal usual care (OUC) comparator has 15.19 life years (LYs) and 7.64 QALYs, meaning the average utility is 0.503. For voxelotor, with LYs at 17.30 and QALYs at 8.60, the calculated average utility is 0.497. This 1% difference between voxelotor and OUC incorrectly suggests that there is no benefit of using voxelotor based on ICER's model in terms of the quality of life rather than years lived. This is despite the model's specific design to show that an Hb increase reduces risk of fatigue, stroke, CKD and PH, which lead to significant decrements in patients' HRQoL. The impact of Hb increase goes beyond what ICER has included in its draft report. ICER	***The impact of an increase in hemoglobin was included in the cost effectiveness model. Inputs from the literature were used where possible including on stroke, fatigue, nephropathy/CKD, and pulmonary hypertension. For the other acute and chronic outcomes of interest where there was no information available in the literature, we assumed no direct effect from treatment, but allow for an indirect effect based on reducing stroke, nephropathy/CKD and pulmonary hypertension.***

	should reflect the full impact of Hb levels on outcomes by capturing the effects of Hb on neurocognitive dysfunction, silent cerebral infarction (SCI), end stage renal disease (ESRD) and survival. • Hb increase translates to reduced healthcare utilization and costs. The benefits of an increase in Hb go well beyond a reduction in end organ damage. Specifically, these positive outcomes often lead to avoidance of low-value spending; reduction in transfusions, reduced patient oxygen dependency, and reduction in the use of erythropoiesis-stimulating agents to treat anemia	
5.	By not considering the full effects of improving healthy hemoglobin levels, ICER is underestimating the benefits of an increase in Hb levels and its impact on the disease. Voxelotor provides clinically meaningful benefit to patients with SCD with a manageable safety profile. ICER's clinical rating of voxelotor as 'P/I: Promising but Inconclusive' is inconsistent with the totality of available evidence. Voxelotor, as an HbS polymerization inhibitor, reversibly binds to hemoglobin, stabilizing the oxygenated hemoglobin state. This improvement in Hb levels is a clinically relevant endpoint in SCD and is supported by the American Society of Hematology, evidenced by the FDA's accelerated approval, and supported by numerous clinical studies. ,	***Given the lack of long term safety data, the lack of direct evidence from clinical trials that treatment with voxelotor decreases acute pain crises as well as other acute and long term outcomes, and given that it has not been demonstrated that the hemoglobin-vox complex behaves the same as normal hemoglobin, we continue to believe the evidence base for voxelotor is promising but inconclusive.***
6.	In rating voxelotor as 'P/I', ICER's assessment is inconsistent with the available evidence base. ICER states "voxelotor did not significantly reduce the annualized incidence rate of acute pain crises and did not improve quality of life." The HOPE study collected health related quality of life (HRQoL) information from both patients' and clinicians' perspectives with multiple questionnaires. It is premature to conclude voxelotor does not improve quality of life before all the collected information is fully analyzed. In fact, a 2019 ASCAT conference presentation regarding voxelotor's effect on reducing the occurrence and severity of leg ulcers points to potential quality of life improvements. There are additional studies that further demonstrate HRQoL benefits of voxelotor treatment. , , Ongoing analysis of the HOPE trial and additional studies are expected to provide further evidence on the HRQoL benefits of voxelotor.	***We have revised this language to say that voxelotor has not yet demonstrated an effect on quality of life.***
7.	ICER implies that use of voxelotor does not reduce transfusions, yet studies disprove this. The HOPE trial did not include patients who were on chronic red blood cell (RBC) transfusions at baseline. SCD patients are transfused for a variety of different reasons beyond anemia; in HOPE, most transfusions were performed because of acute vaso-occlusive crises. In a series of case studies where severely anemic patients were offered voxelotor, there was an observed 60% reduction in transfusions.	***We did not identify any evidence suggesting voxelotor reduces transfusions and have noted this as an uncertainty. We note that the 60% reduction cited in this comment came from a letter to the editor describing 7 compassionate use cases with no control arm; it is unclear how the 60% was derived.***
8.	Voxelotor offers good value for patients and the SCD community, if assessed with the appropriate value framework and model parameters. ICER's framework is fundamentally flawed and unable to accurately assess SCD treatments as it misses multiple value components beyond patient costs and quality of life. GBT does not agree with the application of ICER's value framework and its cost-effectiveness model in quantifying the economic value of innovative SCD treatments like voxelotor, which was approved under FDA's accelerated approval pathway. The systemic issues in SCD, previously mentioned in our open	***ICER's value framework includes multiple components beyond cost and quality of life, including comparative clinical effectiveness; potential other benefits to patients, families and society; and relevant contextual considerations. Our report discusses many of the systemic issues faced by people with sickle cell disease, including inequity and health care disparities, and points out that decision-makers may give additional weight to treatments with the potential to ameliorate such disparities.***

	input letter, were not incorporated into the model. In the recently issued ICER 2020 Value Framework, ICER stated that their methodology cannot quantify disparity and equity value in the current framework. This suggests that ICER's value framework is not appropriate for value assessment in SCD. Furthermore, ICER's cost-effectiveness model is ill-suited for orphan diseases such as SCD and for patients who have been historically ignored and underfunded as it disregards other key value components beyond cost and outcomes such as equity value, disease severity, option value, scientific spillover effects, etc.	
9.	Incorporate the impact of SCD on patients & caregivers in the base case. ICER spends a considerable amount of time reflecting on the SCD burden for both patients and their caregivers, yet this is not reflected in the clinical effectiveness and long-term cost-effectiveness assessments. An appropriate value framework for SCD must take on broad societal perspectives, considering the disparity these patients face. Further, health disparity does not revolve solely around the life expectancy (LE) gained by patients; rather, it includes many additional components, such as patient quality of life and that of their caregivers. Hence, the equity value provided by novel SCD treatments goes well beyond LE gained and should be considered in the base case of the value assessment.	***The revised report includes a co-base-case analysis using both health care sector and societal perspectives, as the societal costs of care for sickle cell disease are large relative to direct health care costs, and the impact of treatment on these costs could be substantial. The health care perspective includes quality of life as well as life expectancy impacts, while the societal perspective also includes caregiver impacts.***
10.	Notwithstanding these concerns, as it specifically relates to the model, ICER's cost-effectiveness model requires significant revisions in terms of both model structure and parameters, as outlined below: Do not discount the future years of today's SCD patients. ICER's method of discounting negatively targets outcomes that are important to patients by over-discounting benefits that occur after the first year of treatment. Considering a 12-year-old child beginning treatment for SCD, a 3% annual discount rate more than halves actual outcomes (55%) after two decades of treatment. By age 45 (the median age of death), health benefits are worth only slightly more than a third (38%) of their value. In ICER's own sensitivity analyses, eliminating discounting more than halves the cost per quality adjusted life year (QALY) gained in the base case, suggesting a substantial impact of the discount rate on overall results. Even in the U.K., one of the toughest markets to access treatment, there is the application of a lower discount rate for outcomes in treatments that, "provide substantial effects in restoring health, sustained on a very long period."	***To account for time value and ensure comparability across studies, discounting is a standard method in economic modeling. In the US, this standard approach has been confirmed by the Second Panel on Cost-Effectiveness in Health and Medicine as a uniform discount rate of 3% applied to both costs and benefits. The use of a 3% discount rate in the US as standard for both costs and outcomes are based on estimates of the real consumption rate of interest and data on real economic growth, which are thought to reflect the social rate of time preference. The use of a single, uniform discount rate for all assessments allows for consistent comparisons across different or prior evaluations.***
11.	Employ structural changes by including the impact of Hb on ESRD and SCI and by considering the impact of baseline Hb on incidence rates of acute and chronic conditions. ICER should add SCI and ESRD to the list of outcomes considered in the model. Additionally, ICER needs to control for baseline (BL) Hb to ensure an accurate reflection of voxelotor's benefit in its model. Not all of the source studies referenced in the model had a baseline Hb similar to the HOPE study (BL mean Hb 8.6 g/dl). Baseline hemoglobin plays a central role in incidence rates of acute and chronic conditions.	***The model includes the impact of hemoglobin on CKD and stroke which include the costs and consequences of ESRD and SCI. We agree that studies have different baseline Hb so we have used the most optimistic effects of Hb on CKD, stroke, fatigue, and pulmonary hypertension that could be found in the literature regardless of their baseline Hb in an effort to estimate the most optimistic benefit of treatment.***
12.	Correct the overestimation of voxelotor's costs. Voxelotor's costs must be uniform throughout the report, yet ICER uses several values for the annual cost of voxelotor ($104,357, $84,000, $99,197). More consistency and clarity are needed. Also, since each voxelotor bottle is a 30-day supply, ICER overestimates voxelotor's annual cost: 12 bottles and 5-6 pills are needed rather than 13 bottles annually, which carries over into the following year. Overestimation of voxelotor's costs incorrectly lowers the modelled benefit. In addition, the value-based pricing calculations of the three drugs in the draft evidence report are	***The cost of voxelotor is calculated in two different ways in the Evidence Report, 1. for a patient that receives treatment for a year, 2. the average cost of treating a cohort of patients for a year given that 27% discontinue in the first year. We have tried to clarify this in the report. The cost of voxelotor is not calculated per bottle but per pill. So the annual cost for a patient that completes a full year of treatment with***

	not consistent with the base case model results, which calls into question the internal validity of the report.	***voxelotor is $10,417 per bottle / 30 pills per bottle X 365.25 days per year X 27% discount = $92,584.***
13.	Correct the underestimation of end organ damage costs. ICER uses MarketScan analyses of SCD patients for its model, which includes commercial and Medicare populations and supplements this with CMS Medicare data. This approach excludes Medicaid data, which account for more than 50% of SCD patients, and severely underestimates the cost of EOD. ICER should refer to the Xue et al., ASH 2019 presentation for guidance.	***Increasing the costs of end organ damage increases the benefit of treatment per event, but also increases the cost of keeping people alive. Sensitivity analysis demonstrates that increasing the costs of end organ damage increases the ICERs for each treatment. We chose the lower costs from the MarketScan data since this was most optimistic for the treatments.***
14.	Revise the SCD baseline utility score to represent U.S. SCD patients so that they are not deprioritized over patients with other diseases. ICER underestimates the baseline utility of patients entering the model. Specifically, ICER derives their baseline utility of 0.71 from a U.K. study, a misinterpretation of this study, where the EQ-5D actually estimated a utility of 0.89 in SCD patients not experiencing pain crisis in the U.K. , In addition, there should be a further adjustment to account for the numerous studies that demonstrate differences in utilities between countries for even the same disease. , , Using a lower baseline utility reference from the U.K. decreases the value of SCD treatments for U.S. SCD patients. Even patients who have returned to the model's baseline disease state can never achieve the total absolute QALY gain of patients with other diseases.	***The baseline utility used in the draft model was the average of utility of two US populations. We agree this a low baseline utility for people with SCD, and we heard from SCD community that higher numbers were not adequately representing the severity of disease. With further discussion with patient groups we have increased the baseline utility to 0.8 to provide an optimistic result.***
15.	Correct the estimated baseline prevalence rates of end organ damage in the modeled population. The baseline prevalence rates for end organ damage for a 24 year old patient with SCD have been overestimated and are not consistent with clinical practice and literature. This failing does not leave much room for future interventions to improve the condition. In fact, the risk of end organ damage increases as patients age. ICER's use of MarketScan analyses of SCD patients for its model includes only commercial and Medicare populations, excluding Medicaid data (which, as mentioned above, constitutes more than 50% of SCD patients). Further this misrepresents the prevalence rates of acute and chronic conditions for younger patients as only 9% of all SCD patients between 18-30 are Medicare or dual eligible beneficiaries: this undervalues the impact of voxelotor. By not including such a patient population, ICER does not account for the reality of care and outcomes in SCD.	***Baseline data used to estimate the prevalence of chronic conditions comes from the MarketScan data. Risk was estimated by age subgroups to capture the increasing risk with age. As mentioned, this data has fewer Medicaid patients which is likely to underestimate the prevalence of chronic conditions in this population. We considered this assumption appropriate as it is optimistic for treatments.***
16.	ICER's inaccurate estimation of prevalence of end organ damage makes the outcomes of patients on voxelotor two times worse, significantly underestimating the value of voxelotor. Correct the underestimation of 1 g/dL Hb increase's impact on risk of end organ damage. The impact of Hb on risk and burden of stroke are underestimated in the model, decreasing the estimated value of voxelotor. Stroke's impact on HRQoL and costs should be considered both acute and chronic. The impact of 1 g/dl on risk of stroke using the COOPERATIVE study should also be adjusted for genotype distribution and type of stroke, hence an odds ratio (OR) of 0.583 per 1 g/dl increase in Hb should be employed instead of ICER's value of 0.602.	***Unfortunately, the treatment effects for voxelotor were not reported by genotype so we could not investigate these subgroups.***
17.	The impact of Hb on risk of PH is severely underestimated. ICER uses the Caughey et al. study, which reports -1% of the delta in prevalence of elevated pulmonary artery systolic pressure (ePASP) observed between patients with mean Hb >8.8 g/dl vs. <=8.8 g/dl, not necessarily for a 1 g/dL change in Hb. In contrast, many other studies have estimated the OR of having an elevated tricuspid regurgitation	***TRV on echo does not correlate well with catheterization proven PH. Further it is not independently associated with increased morbidity. (Hebson et al.)***

	velocity (TRV) per 1 g/dl increase in Hb, which gives a weighted average OR of 0.600 per 1 g/dl increase in Hb as opposed to the 0.97 calculated OR employed by ICER. , ,	
18.	These two above mentioned incorrect OR values combined, inflate the cost per QALY gained of voxelotor vs. optimal usual care by nearly 60%, which further decreases ICER's estimated value for voxelotor. Correct the estimation of the rate of mortality of patients with SCD in the model. SCD patients have a devastating prognosis compared to the general population, and the model should accurately quantify their life expectancy. An accurate mortality rate is crucial as its overestimation will make a treatment appear less effective. ICER overestimates the mortality rate by: 1) Adding end organ damage such as stroke, CKD and PH mortality on to measures that already capture this in real-world SCD mortality rates. 2) Overestimating the impact of end organ damage on mortality	***The rates of death used in the model were adjusted for the risk of death from end organ disease. The predicted life expectancy for patients on usual care in the model was 43 years, which is very similar to other published studies.***
19.	CKD: ICER assumed the CKD impact on mortality to have a relative effect of 9.57 based on a study conducted by Dr. Lanzkron, which misinterprets her analyses. The value ICER uses is the impact of having renal disease on the age of death of patients, not the impact on mortality rate. Literature suggests the relative risk to be 1.42. , PH, HF, and MI: ICER assumed the PH impact on mortality to have a risk factor of 12.57, with heart failure (HF) and myocardial infarction (MI) assumed to have the same effect. 12.57 is based on reference studies that defined PH based on an echocardiogram. However, the gold standard for defining PH is based on heart catheterization, wherein the excess risk of death of PH vs. non-PH patients is 2.46. Combined, the two factors above contribute to an assumption of an excess risk of death, and by doing so more than double the cost per QALY gained.	***Reducing the risk of death from these chronic conditions as suggested will increase the ICER, making the treatments less cost-effective. We chose to use the highest estimates of the risk of death to give an optimistic estimate of the treatment effect.***
	Conclusion ICER's value framework, including the evaluation of clinical benefit and application of traditional cost-effectiveness modelling, ignore the severity of the unmet need in SCD, and the potential of novel disease-modifying therapies. Extraordinary pain and fatigue, reduced life-expectancy, poor treatment options and inequity as compared to other diseases is the base case for SCD patients. Value assessments for new treatments in SCD must accurately and comprehensively capture the full benefit delivered to patients and their families, or we risk continued under investment in one of our most ignored diseases	***ICER's report includes assessment of the impacts of these treatments on symptoms and life expectancy, but also look beyond clinical effectiveness and cost-effectiveness to include a comprehensive assessment of these interventions, including other benefits and contextual considerations that may be impacted by conditions and treatments.***
Novartis		
1.	CHALLENGES SURROUNDING COST-EFFFECTIVENESS ANALYSIS IN SICKLE CELL DISEASE IN THE UNITED STATES (US) Cost-effectiveness analysis (CEA) is a well-known approach to measuring the value of new health interventions. Within this approach, The Second Panel on Cost Effectiveness in Health and Medicine recommended measuring health effects in quality-adjusted life years (QALYs).10 Despite this recommendation, measuring the value of new SCD treatments is particularly challenging for both contextual and technical reasons. Admittedly, ICER acknowledges many of these limitations within their draft report. In Section 5.1 of the draft report,9 for instance, ICER notes that it is not possible to capture the full psychosocial impact of systemic issues, such as racism.9	***Thank you for your comment. Our report attempts to discuss many of the systemic issues faced by people with sickle cell disease, including inequity and health care disparities, and points out that decision-makers may give additional weight to treatments with the potential to ameliorate such disparities.***
2.	The technical limitations of CEA in SCD include inconsistent evidence and an evolving understanding of SCD's wide-ranging and complex impacts. In addition to these technical limitations, there is no consensus on, and	***We agree that there is currently "no consensus on, and no validated methods exist for quantifying the value of other important aspects (e.g., potentially reducing inequality,***

	no validated methods exist for quantifying the value of other important aspects (e.g., potentially reducing inequality, impact on family planning decisions).	***impact on family planning decisions)," and therefore include qualitative assessment of these factors as potential other benefits and contextual considerations.***
3.	Modelling the value of Adakveo using a CEA model in the US is particularly problematic for the reasons described in the table below.(next sheet) Table 1: Overview of limitations of CEA modeling for Adakveo (crizanlizumab-tmca)	***Please see our responses to your specific comments below.***
4.	The overall benefit of reducing VOCs is not fully captured in ICER's model, as critical evidence is evolving SCD substantially shapes patients' daily lives, including emotional and physical wellbeing, relationships, education, and work.11 VOCs are the hallmark of SCD.2 In a recent global survey, patients with SCD experienced an average of 5.2 VOCs per year, resulting in frequent hospitalization.11 Yet pain is difficult to measure; in fact, there are no objective diagnostic tests for measuring VOCs, as a clinical diagnosis is required.12,13 Research presented during the American Society of Hematology (ASH) 2019 Annual Meeting shows that the QoL of patients with SCD measured in the form of utility is 20% lower during a VOC compared to previous estimates14, (i.e., utility during crisis is 0.311 in recent research14 vs. previous estimate of 0.39 from Anie et al. [2012]15).	***We use the reported treatment effect on pain from the SUSTAIN trial and apply optimistic assumptions to capture the treatment effect on health related quality of life which includes aspects of daily activities, anxiety and depression, pain and mobility. In the societal analysis we have also used optimistic assumptions to estimate the impact on school attendance, caregiver burden and lost productivity.***
5.	ICER should use the average weight of the patients in the SUSTAIN randomized clinical trial when calculating the cost of treatment with Adakveo The mean weight from the crizanlizumab 5mg/kg arm of SUSTAIN trial (69.46 kg)16 should be used to estimate the number of doses of Adakveo, and consequently, the cost of treatment with Adakveo. Instead, the ICER draft report appears to use a general-population weight for dosing and cost of treatment calculations; however, patients with SCD typically weigh less than the general population. For example, a real-world study of patients at the Montefiore Medical Center in New York found, that the average weight of a patient with SCD was 61.0 kg for patients aged 21-30 and 63.7 kg for patients aged ≥40 years.17 Further, given the ages of patients in the SUSTAIN trial (16 to 63 years of age), 7 their mean weight should inform the assumption of the cost of treatment with Adakveo for the majority of patients with SCD in the real world in the US. Basing treatment dosing on more realistic weight assumptions is needed to accurately calculate the dosing and cost of treatment with Adakveo in the real world. QALYs underestimate the short-lived but intense experiences such as VOCs and therefore undervalue the beneficial impact of Adakveo While quality-adjusted life years (QALYs) are a useful metric for CEAs in other disease areas, the Second Panel on Cost Effectiveness in Medicine notes that: "QALYs may not accurately reflect the burden of short-lived but intense experiences. Thus, the benefits of interventions that reduce the incidence of such experiences may be undervalued."10 Clearly, VOCs fall into this category. Society places a high value on health gains for patients with severe disease People are willing to give up aggregate health to give priority to patients with more severe disease that have a significant impact on patient QoL.18 Governments and health policy bodies in some European countries have started to incorporate considerations based on disease severity and small patient populations into their guidelines for evaluation of new technologies.18 Differences in how such factors are accounted for lead to wide variation in value estimates across	***While one study using data from the average weight of a real-world study of patients at the Montefiore Medical Center in New York found that patients with SCD are lighter than the general population, other studies have shown that: 1) adult patients with SCD are similar to the general population, with 4% underweight, 42% normal weight, 26% overweight and 28% obese; and 2) children with SCD are similar in weight to the general population at birth and then "fell away before catching up at around 15 years of age in girls and 18 years in boys ". To keep with our efforts to be optimistic we have used the lower adult average weight as reported in the SUSTAIN trial.***

	international HTA agencies. Society values QALY gains more if the treatments also reduce inequality. However, measuring the value of improved health equity is challenging due to the wide scope and lack of agreed upon normative framework. In the US, the burden of SCD is borne primarily by ethnic minorities, particularly African Americans. In addition, a majority of adult patients with SCD are in the lowest income quartile and are covered by Medicaid, as the debilitating symptoms of SCD can make finding and retaining employment difficult. Subsequently, patients with SCD and their families tend to have lower incomes. Further, 31.1% of US physicians are not accepting new Medicaid patients, and studies have shown that patients with SCD covered by Medicaid may have less access to health care and receive lower quality care. These factors combine to exacerbate disparities in health care for patients with SCD. TRADITIONAL CEA FAILS TO ACCOUNT FOR WIDER SOCIAL AND ECONOMIC IMPACTS OF SCD TREATMENT Typical CEA studies do not consider a variety of important benefits, whether due to measurement difficulties, or a narrowly defined perspective. SCD has particularly wide debilitating impacts on patients that are not captured by traditional CEA.	
6.	SCD has a significant negative impact on family and marriage decisions As ICER has noted, "Some patients and family members described making decisions to avoid marriage to maintain health insurance or forego having children to avoid passing on the gene to the next generation."32 Quantifying how Adakveo would affect these decisions and the value of any changes in decisions is difficult, and accounting for such in CEA is challenging.	***Thank you for your comments.***
7.	The debilitating physical effects of SCD inhibit educational achievement, limit career opportunities, development, and earning potential Productivity costs are the most frequently included indirect cost in CEA.30,31 Recent research has shown that patients with SCD have substantially lower lifetime earnings compared to similar individuals without SCD.33 SCD in general and VOCs specifically are associated with work productivity impairment and impact patients' ability to participate and remain in the workforce. In the US, patients with increased frequency and severity of VOCs reported significantly greater absenteeism and overall productivity loss. Patients with SCD with ≥4 VOCs have a 47% chance of applying for disability compared to only 12% for patients with SCD with 0 VOCs.34 Despite a desire to work, patients with SCD have high rates of unemployment. SCD can prevent individuals from completing their education and advancing in their career.26 Moreover, ICER has noted that some caregivers leave the workforce to provide care, resulting in additional economic costs.9	***Using published data and data from the Sick Cells survey, we have undertaken a societal perspective which captures impacts on lost productivity, caregiver burden and school attendance.***
8.	SCD entails significant caregiver and family burden The chronic pain caused by SCD may lead to emotional and behavioral changes that affect the lives of family members, friends, and colleagues.35,36 Caring for a person with chronic pain can lead caregivers to experience physical and psychological health impairments, decreased relationship satisfaction, and lower QoL.37 Studies of caregivers of children with SCD found they suffer from disease-related parenting stress and have significantly higher depressive mood scores. While parents are typically the caregivers for children with SCD, for adults with SCD, caregivers may be spouses, relatives or friends, whose burden may be underestimated in ICER's model.	***This has been captured in our updated societal perspective analysis.***

9.	The lack of alternative treatment options means that patients with SCD have above-average opioid exposure and consequent risk of dependence Due to acute and chronic pain, patients with SCD are frequently exposed to opioids.40,41 In a study of Texas Medicaid recipients, 58.7% of patients with SCD had ≥1 opioid prescription, with a mean of 4.2 prescriptions over a 12-month period. Multivariate analysis examining the relationship between VOC events and opioid use reported that for every increase in VOC event, the number of opioid claims increased by 9.5% (incidence rate ratio = 1.095; 95% CI, 1.078–1.111; P < 0.0001).40 Another study found that 65% to 70% of Medicaid recipients with SCD and 54% to 57% of commercial insurance-covered patients with SCD had an opioid prescription in a given year.41 While patients with SCD are not at increased risk of opioid pain reliever-related death compared to opioid users with other diseases,42 those individuals who do abuse opioids can impose substantive direct and indirect costs. 43	***Thank you for your comments.***
10.	CLOSING REMARKS Novartis recognizes the need for a holistic, evidence-driven approach to determining the value of new treatments, which incorporates clinical outcomes, patient experiences, benefits to the healthcare system, and societal value. We are confident in the value that Adakveo brings to patients with SCD, as well as society, particularly through the significant reduction of VOC, which is the hallmark of the disease. Novartis commends ICER for the extensive efforts to index individual determinants of the value of Adakveo, and quantify their complex interplay. However, we note that there continue to remain significant methodological challenges for estimating the value of new treatments in SCD in the US via CEA, challenges which we consider substantial at this time within the CEA framework.	***While challenges exist in CEA for sickle cell disease, clinicians and insurers are still faced with decisions about how best to use and provide access to these new therapies. This ICER review is the most comprehensive to date and should be used to evolve the ongoing evaluation and public dialogue in this important disease area. Further, we hope our review will highlight the significant gaps in the evidence base and encourage manufacturers and government agencies to invest in these patients by funding studies on quality of life, acute and chronic outcomes, and impacts to productivity.***
Patient/Patient Groups		
Cayenne		
1.	First is the fact that due to the extreme, unbearable pain, many patients are unable to work and/or attend school. Working gives people a sense of identity, belonging and quality of life. Education allows people to better themselves and their families' lot in life. If there is a treatment that can assist patients with staying out of the hospital to be able to work and/or go to school, it is paramount to give them access to such treatment. Second, as a result of the pain, patients inevitably endure depression, hopelessness and loss of the desire to live. Some have even said, "I would be better off having cancer or HIV/AIDS because at least I wouldn't be discriminated against." This thought should never come to mind in any patient. If there is a treatment that can reduce the occurrence of pain episodes and hospitalizations, it will inevitably allow patients to have a sense of hope and purpose, then I say give them access to this life-changing treatment. Third, the constant damage that the sickling wreaks havoc on various organs, resulting in a diminished quality of life. If there is a treatment that can slow the effects of sickling so that patient's quality of life is extended, then again I say, it is paramount give them access. The drugs illustrated in your report, crizanlizumab and voxelotor, have the potential to improve the quality of life and extend life for SCD patients. What concerns me is why would anyone want to interfere with any person having quality of life? Why would anyone want to interfere with a person's ability to turn depression and hopelessness,	***Thank you so much for sharing your experience with us. As stated in the report, we believe that the approval of these drugs for Sickle Cell Disease represents an important advancement for patients and their families. You are very important, and you matter. Our goal is to convene a public meeting where all stakeholders can openly discuss the issues around a fair price for these new therapies, fair access to these new therapies, while also preserving the incentive for companies to continue to develop promising new therapies.***

	into joy and thankfulness? Why would anyone want to interfere with a person's ability to work/go to school and contribute to society? Why would anyone want to interfere with a person's ability to finally have dignity and not be constantly beaten down? Dr. Pearson, you can make history. For the first time in our community, YOU can be that person that considers the unmeasured costs of Sickle Cell Disease before releasing your evidence report in March. YOU can strongly emphasize the significant immeasurable value of patient quality of life and improvements in life expectancy. YOU can tell our community that Sickle Cell Lives Matter. That they matter. Dr. Pearson, YOU can tell me that I matter as I am also an individual living with Sickle Cell Disease.	
Martin Center for Sickle Cell Initiative		
1.	As you stated repeatedly in your report, SCD is a multi-faceted condition that can cause extreme hardships on patients and their families. At MCSCI, we bear witness to these hardships daily. We see how SCD's impacts on patients vary dramatically from person to person but that they have multiple periods of severe pain in common. We see that they share other things to varying degrees, things like a life with uncertain length; lowered educational attainment levels, diminished economic opportunity; periods of depression and hopelessness; and so many other issues that have a negative effect on their quality of life. This begs us to ask the question, "how can anyone place an economic value on any of these things? Yet, it seems that this is what your report has the possibility of doing when viewed only on its surface	***The goal of a cost-effectiveness analysis is not to place an economic value on a person or a person's suffering. The goal is to better understand the value of a treatment given how well it performs and how much it costs, compared to all other drugs for all other diseases.***
2.	We give you credit for confirming that the values of "…education, ability to work, the effect on caregivers and other costs" have societal benefits that the report has not yet measured. Yet, even though you acknowledge that "these additional societal benefits not currently included in the health care perspective are important for understanding the full potential impact of treatments and their value," the net effect of the report is that it still places negative values on the three therapies you analyzed. We are afraid that, after reviewing the report, payors whose only interest is in economics will likely be persuaded to be reluctant to cover these therapies and/or refuse to cover them altogether.	***We have included cost effectiveness models taking into account both a healthcare perspective and a societal perspective. In addition, we have provided a number of scenario analyses to help the reader understand how different assumptions could impact the current estimates. Our goal is to bring increased transparency to discussions around price and access so that all stakeholders, most notably patients and clinicians can have a seat and voice at the table when these discussions are taking place.***
3.	Your report summarizes that crizanlizumab has the potential to extend life by 2.4 years, that voxelotor could extend life by 2.1 years and the L-glutamine might extend life by approximately 1 year. We ask, "what is the value of those additional years to the patients, their families, their friends and their neighbors?" We think the answer is that the value is immeasurably higher than any one person or any one scientific analysis can quantify. It is our belief that any improvement in care and each gain in life quality, no matter how incremental they may be, is of significant value to every person affected by SCD. As a point of reference, I lost my wife of 12 years due to SCD complications in 1989 when she was only 36 years old. That was over 30 years ago but not a day goes by that I don't wish I could have had just a little more time with her.	***We are very sorry for your loss and we appreciate you taking the time to provide comments. We agree that incremental improvements can be invaluable to patients and their families. Our goal is not to place a value on anyone's life. Our goal is to better understand the value of a new therapy based on how much it actually helps patients and how much it costs.***
The National Minority Quality Forum		
1.	Two new therapies (crizanlizumab and voxelotor) and one relatively new therapy (L glutamine) have become available for patients with sickle-cell disease (SCD). ICER undertook an assessment to evaluate "the clinical effectiveness and cost effectiveness of crizanlizumab,	***Thank you for your comment. We agree that the value of a therapy to an individual patient is very important and different than value as determined by cost effectiveness. "Clinical"***

	voxelotor, and pharmaceutical-grade L glutamine for patients with SCD." Although ICER recognized that each of these drugs has novel clinical effectiveness that could reduce pain and suffering and improve quality of life for SCD patients, it did not find that any of them to be a high-value medication according to its cost-effectiveness criteria. This failure to meet ICER's criteria for high value has little to do with the drugs value to SCD patients. From the perspective of patients and their physicians and caregivers, ICER's value metrics introduce questionable benchmarks that distort the definition of high medical value as it is commonly understand.	***value – value to the patient – is not the same thing as what we call "long-term value for money." We add the "for money" part to make that clear, and our separate ratings on comparative clinical effectiveness seek to capture the strength of evidence to demonstrate the clinical value of a treatment. For more information on these important differences you may want to see https://icer-review.org/material/2020-value-assessment-framework-final-framework/***
2.	The Forum's values are predicated on two axioms: (1) Every patient should have access to appropriate care, and (2) health systems and their treatment protocols should not elevate a patient's risk for a poor outcome or a poor quality of life. Summarized: Do no harm. Based on these predicates, we view treatment plans, policies, assessments, or value judgements that deny access to appropriate care as social determinants of health, and we see their negative consequences as reportable events. ICER operates from a different frame of reference. Fundamental to every one of ICER's assessments is the application of its benchmark cost thresholds to help it distinguish high-value from low-value care. A medication that is inferior in its medical benefit, but whose cost meets ICER's long-term money value and short-term affordability valuation could be designated high value compared with a more clinically effective, but more costly, medication. A more costly, but clinically effective, medication could be rated as low value in the ICER assessment. ICER conveniently ignores that clinical effectiveness and lowering of patient risk are inextricably linked, and cost does not mediate that relationship. ICER is an advocate for health-care systems that regard structural inequalities as acceptable by-products of value assessments that promote the elevation of a patient's risk for a poor outcome or a poor quality of life in order to avoid exceeding cost thresholds. Working from its financial model, ICER withholds a high-value assessment for any of the three novel SCD treatments because the cost exceeds ICER's predetermined cost thresholds, providing dubious justification for health systems to limit or deny access to these medications. The Draft Report does not suggest that the withholding agency seek a patient's consent to this care limitation or suggest the appropriateness of reporting the negative consequences of the policy. The Forum sees no useful purpose in trying to deconstruct the ICER value assessment to show that flaws, inconsistencies, and inequities disqualify the Draft Report as a useful assessment of the value of these new treatments for SCD. Actually, ICER's assessment model succeeds at what it is designed to accomplish: to determine whether any of the medications meets its narrow definition of high value by having a market price that does not exceed its benchmark cost threshold. We disagree with the premise that medical value must be a function of cost. The corollary of that premise is a tiered health-care system where patient risk is deliberately elevated and inequities are commonplace. The US Food and Drug Administration by its approval and ICER by its own evaluation have determined that the three SCD medications are clinically effective. Our root-and-branch rejection of the ICER Draft Report is founded on the operational assumptions that are the report's underpinning. They are antithetical to our value, fundamental to medicine, which we summarize as do no harm. ICER and the Forum have different opinions, based on different values; we	***We too believe that every patient should have access to appropriate care and that care should not increase a patient's risk. We do not believe that beneficial care should be withheld by clinicians nor lack coverage from insurers. The difference in our view is that the price of a new drug is largely at the discretion of the manufacturer and not necessarily related to how well it improves health for the price. Under this view, the responsibility to assure access to beneficial treatments must be shared by insurers and drug makers. It is that balance between clinical value and what a fair price would be that drives our hope that prices aligned with patient benefit will lead to IMPROVED access, and that it will also help us create an overall cost structure for health insurance that can guarantee affordable access for all individuals.***

	believe that our values more closely align with what any SCD patient (or any patient, for that matter) would expect of the health-care system. Providers that build their SCD-treatment plans on the ICER Draft Report without informing patients of its inherent limitations not only will violate a trust relationship but also will introduce inequalities and poor health outcomes into their systems while diminishing the quality of life for those who come to them for care. ICER and the Forum have different opinions, based on different values; we believe that our values more closely align with what any SCD patient (or any patient, for that matter) would expect of the health-care system. Providers that build their SCD-treatment plans on the ICER Draft Report without informing patients of its inherent limitations not only will violate a trust relationship but also will introduce inequalities and poor health outcomes into their systems while diminishing the quality of life for those who come to them for care.	
Partnership to Improve Patient Care		
1.	The QALY is a Particularly Inappropriate Metric to Evaluate Treatments for SCD PIPC has highlighted the discriminatory nature of the QALY, as well as the limitations of the metric as a measure of health gain, in many previous comments on ICER assessments. Given the complex nature of SCD, its severity, and the fact that the burden disproportionately falls upon specific groups within society, the QALY is a particularly inappropriate method for evaluating any value accrued from interventions aimed at its alleviation.	***The QALY is the gold standard for measuring how well a medical treatment improves and lengthens patients' lives, and therefore has served as a fundamental component of cost-effectiveness analyses in the US and around the world for more than 30 years. Because the QALY records the degree to which a treatment improves patients' lives, treatments for people with serious disability or illness have the greatest opportunity to demonstrate more QALYs gained and justify higher prices. Moreover, to be responsive to the concerns about the QALY, ICER now incorporates a calculation of the Equal Value of Life Years Gained (evLYG), which evenly measures any gains in length of life, regardless of the treatment's ability to improve patients' quality of life. More information can be found here: https://icerreview.org/material/the-qaly-rewarding-the-carethat-most-improves-patients-lives/.***
2.	Numerous studies have highlighted how key factors such as severity of disease, pain levels, and sparse availability and limited effectiveness of alternative treatments — all relevant for SCD — are considered as key determinants of priority in health care settings. , In fact, some health technology assessment systems in European countries such as Norway, Sweden and the Netherlands actively use information on these factors to inform approval decisions for new medicines, given the limitations and simplicity of the QALY as a measure of health gain.	***These considerations are core components of our value assessment framework and are discussed in the chapter on Potential Other Benefits and Contextual Considerations. They will be deliberated and voted on at the public meeting of the New England CEPAC on March 26 as a way to signal to policymakers whether there are important considerations when making judgments about long-term value for money that are not adequately captured in the analyses of clinical and cost-effectiveness***
3.	Additionally, health state valuation studies that translate into QALYs are undertaken in predominantly white populations, and weighting calculations are largely constructed using linear regression which over-homogenizes weights around the mean. The selection and construction of the 'domains' that make up quality of life tools were constructed by a small group of white men twenty years ago in Switzerland. No one has challenged these sets to be updated, as it would be inconvenient for the method, but it is very clear that this type of metric is highly inappropriate for ICER to use in evaluating a	***The quality of life values used in this analysis were derived from EQ-5D data that had been collected from sickle cell patients. THE EQ-5D is a well-accepted and standardized, generic instrument that has been used in multiple populations and countries around the world.***

	treatment for a disease that disproportionately impacts people of African and Hispanic descent. If access and approval decisions around new healthcare technologies are made based on metrics that treat patients as averages like the QALY, and these averages are driven by regression towards majority populations, minorities within the population will ultimately suffer the most	
4.	Standard of Care is a Faulty Comparator, as it Does Not Truly Exist for SCD ICER chooses to use the comparator of "usual care," which is neither standardized nor considered comprehensive care for SCD. SCD is a syndrome of diseases and care for any two patients can look markedly different depending on disease subtypes and the unique complications experienced by each patient. ICER even acknowledges in its report that "baseline or usual care for patients with SCD is highly variable and represents a failure in the US health care system." Despite this recognition, ICER continues to utilize methods that do not adequately account for this variability.	***Thank you. We have acknowledged this uncertainty in multiple places of the report (e.g., 4.3 Uncertainty and Controversies, 5.2 Treatment Strategies)***
5.	SCD patients are a largely underserved population. There is a lack of specialists and clinicians with expertise to treat SCD, leading patients to seek care from generalists who are often not equipped to help patients manage their disease. Due to the lack of standardized care for SCD, treatment plans administered by generalists often vary drastically depending on the unique characteristics of each patient. Furthermore, non-specialists also often assume SCD is a pain condition, which can lead to inappropriate treatment for the disease's complications.	***Thank you. This is important context that was described in Chapter 2 of the report.***
6.	ICER Chooses to Use Claims Data Instead of Listening to Input on Standards of Care from Patient and Clinician Stakeholders ICER's report uses claims data to determine the number of acute pain crises (APC) in SCD patients. Administrative and accounting data sets such as claims data sets have the advantage of being real-world data that are more likely to reflect 'actual' cost data than the more traditional ingredients approach. Nevertheless, there are many variables for which administrative data are noted as being poor proxies. Data not reflecting service over- or underutilization and ineffective coding procedures are common flaws in administrative data This issue holds particularly true in evaluating APC for SCD. When you speak to SCD patients or clinicians they will tell you that the standard of care is to handle most APC in a home setting, not through hospital admission. The American Society of Hematology (ASH) noted this to ICER in its first comment letter, stating that "many patients manage both their acute pain and chronic pain at home. Adequate management of acute and chronic pain associated with SCD is an ongoing challenge both for patients and the clinicians responsible for their care." This assertion from the patient and clinician community is backed up by studies that show patients managed the majority of their APC at home versus in a hospital setting. With this in mind, claims data will drastically underestimate the typical prevalence of APC events for SCD patients.	***Input on standards of care were obtained through input from clinical experts, published clinical practice guidelines, and patients. The definition of pain crisis used in this report was the same as that used in the clinical trials. Baseline numbers of acute pain crises were taken from the clinical trials.***
7.	The Assessment Fails to Capture Outcomes that Truly Matter to SCD Patients. As is typical in ICER assessments, both of the trials undertaken to evaluate quality of life effects and the studies from which the model utilities are sourced were undertaken using generic patient-reported outcome (PRO) tools, the EQ5D and the SF36, rather than disease specific tools. SCD carries a large disease burden that is not adequately captured	***We encourage product manufacturers to use disease specific measures of quality of life and utilities in their pivotal trials. In order to fill some of the gaps in evidence you outlined, we partnered with Sick Cells to help them design a questionnaire to better assess and quantify issues that matter most to patients. The results***

	using generic PRO tools. As a group of SCD stakeholders shared with ICER in their initial letter, "[t]he debilitating nature of SCD impacts social relationships, employment, and the educational attainment goals of patients….Likewise, there are notable financial and emotional burdens on the caregivers and families of patients with SCD." Given the massive disease burden of SCD, specific PROs should have been used and an attempt should have been made to capture other cost factors — hospitalization, lost productivity, caregiver burden, etc. — in the base case, not just the contextual considerations. There have been numerous studies suggesting that generic PRO tools such as EQ5D are poor at measuring marginal changes in quality of life effects across health states, and that they are particularly poor measures of quality of life in SCD. This brings us back to our previous point about the QALY. It is imperative when evaluating treatments for a disease as complex as SCD that disease-specific metrics are used.	***of that survey have been incorporated into the report including the economic model.***
8.	ICER Makes Faulty Assumptions About Lifetime Cost of Treatment ICER's model makes the assumption that patients will be using these new drugs under optimal prescribing conditions non-stop from the age of 24 years through to death. This is highly unrealistic. It is typical in drugs taken for chronic conditions for patients to take treatment holidays, often when the treatment is effective, and at times when it is ineffective, as agreed by their physicians. It is also true that drug use — especially of specialized drugs — falls away later in life when pain relief and symptom management become more common. In addition, ICER assumes that the price of these treatments will remain the same for the next 20 years, which is very unlikely. What is more likely is that generic substitutes will enter the market, driving down prices. If you factor in this steep drop in price after 10-15 years, ICER's cost estimates would drop dramatically. ICER also does not factor in savings from reducing the incidence of expensive hospital care, which would impact the assumed lifetime cost of treatment.	***Cost-savings from expensive hospital care are included in the model. Continued treatment is based on the treatment indications. No effectiveness data has been provided on treatment holidays so the model also make the optimistic assumption that patients will have a continued treatment effect.***
Patients Rising Now		
1.	Overall, we concur with the draft report's statements that "a broad appreciation for the impact of SCD on the lives of patients and their families must be achieved and must be kept front and center when making judgments about the value of these treatments." And "What is certain, however, is that the introduction of new, effective treatments for SCD serves as an opportunity for the overall care of patients with SCD to be re-imagined and improved from top to bottom." We strongly hope that ICER and its advisors deeply embrace those concepts as part of the fundamental value of the new treatments for SCD. Patient and Caregiver Perspectives and Issues We appreciate ICER's thoughtful description of SCD's impact on people's lives – both patients and their caregivers – in the Background and Patient Perspectives sections. We also applaud ICER for improving its standard operating procedure to include a Patient Perspectives section in all its reports moving forward. We share ICER's concern about the lack of information about quality of life (QoL) data from the clinical trials ICER reviewed for the draft report. We would have appreciated more discussion about whether that lack of data – or findings of non-significant improvements in QoL measures in the clinical trials – are due to methodological problems with the trials, problems with the measures used to evaluate QoL, or some other factors. We are hopeful that the survey ICER, Sick Cells and the Sickle Cell Disease Association of America (SCDAA) are conducting	***Thank you for your comment.***

	will provide greater insights into how to better measure QoL for people with SCD and their caregivers. (See more about this survey below.)	
2.	We concur with the draft report's statement that new treatments hopefully "will allow students to attend more school, will decrease the number of missed days from work, will have fewer demands on the caregiver, and will have lower out-of-pocket costs." We similarly concur with the draft report's statements that "It also seems likely that new, effective treatments could reduce caregiver burden," and "if patients have less pain, suffer fewer morbidities, have fewer hospitalizations, and need fewer doctor visits, then their families and caregivers would have more time to focus on their own education, careers, family, friends, and other interests." Given those forward-looking statements, we hope that the survey being conducted will have appropriate questions and be methodologically robust enough to provide valid insights on those issues.	***The survey was intended to provide ICER with estimates of caregiver and patient burden due to sickle cell disease that are not available elsewhere. Sick Cells and ICER collaborated on a list of questions, including validated instruments of employment and productivity (such as the Work and Productivity Impairment instrument - WPAI). Sick Cells received a total of 509 responses, of which 454 were used in the analysis.***
3.	We find the draft report's discussion about variability in the severity of SCD to be very important, and appreciate the draft report presenting information about people who have more or fewer acute pain episodes. As the report also notes, determining benefits of specific treatments will always require individualized assessments, but until there is more data "the alignment of costs with potential patient benefits for these new therapies is unclear." That is why we strongly believe that decisions about individual treatment plans are best done using shared decision making by people with SCD and their care team.	***We agree that decisions for individual patients are best made by patients and their care team. Decisions about populations of patients at a national, regional, or state level, benefit from additional information about subpopulations. This has been summarized in both the comparative clinical effectiveness section of the report and in various scenarios in the comparative cost effectiveness section of the report.***
4.	Related to individualization of care, we are a bit concerned that the draft reports analysis and methodology does not adequately consider or address the complexity of SCD's multi-organ system manifestations in an integrated manner since that is the reality for people with SCD. That is, people with SCD do not address their disease in a piecemeal or siloed approach, but rather need whole-person care and considerations from their care team. Another important patient perspective that is not adequately discussed in the draft report is the different routes of administration, i.e., IV v. oral. Those difference can dramatically affect patient costs and access, particularly since IV administration may require travel to a clinician's office. We would appreciate ICER more extensively exploring those issues in the final report.	***Thank you for your comment. We acknowledge the important clinical consequence of multisystem organ dysfunction and have chosen the best method to capture this in our economic model. We have also included the costs associated with IV administration versus oral administration in our model.***
5.	Importance of New Treatments for Unheeded Diseases As the draft report notes – and we concur – the population primarily affected by SCD has been marginalized in many aspects of health care in the United States, ranging from access to treatment, to financial support for public health and research. Therefore, we are gratified that the draft report highlights the importance of new treatments for SCD and how these new treatments will help reduce inequity in treatments. Hopefully, the availability of new treatments for SCD will illuminate this issue and foster further discussions leading to more research and better treatments for diseases that disproportionately affect populations that have been underrepresented in access and funding in our society.	***Thank you for your comment. We agree.***
6.	Despite the historical situation, we are heartened that these new treatments for SCD are now available, and that many more are on the way, with about 30 potential sickle-cell drugs in late-stage development, including at least one potentially curative gene therapy. However, we are concerned that if reimbursement or access to the recently approved treatments is problematic, that will result in resources being diverted away from clinical trials and thus delaying or	***Thank you for your comment.***

	killing the development of new treatments. Such an outcome would of course perpetuate the historical marginalization of the people and families affected by SCD, and continue society's disregard for the health care needs of SCD patients and families, and potentially other similar diseases.	
7.	The draft report notes that the availability of multiple new medicines with different MOAs "provides an opportunity to potentially combine therapies to address multiple pathophysiological pathways as opposed to just one. While there is much to be learned about the potential benefits and harms of combination therapy, there remains significant potential for new understanding and hope for additive health benefit for patients. With these new treatment options, a more targeted approach, and the potential to deploy multiple concurrent therapies, comes the potential for a healthier patient." We believe it is very important to explore this likelihood since the trend in modern medical treatment is the use of multiple medications, and the two new treatments also provide different clinical benefits to patients, e.g., as shown in Table 5.24 crizanlizumab reduces acute pain crisis events, and voxelotor reduces incidence of strokes.	***Thank you for your comment.***
8.	Problems of Completeness and Timeliness While we applaud the survey that is being conducted with Sick Cells and SCDAA, we are extremely concerned that ICER released the draft report for comment before the survey results could be included. This is another indication that patient perspectives are an afterthought and a third-tier priority for ICER's analyses and evaluations. We find this particularly problematic since the draft report even states that the survey "may provide valuable information needed to assess the comparative effectiveness of the interventions and help us to better quantify important information on quality of life and productivity." If that is they case, then why not delay the draft report so those results could be included?	***In labeling our report as a "draft" and in allowing an opportunity for public comment, we acknowledge that our draft iteration can always benefit from stakeholder input. The survey development initiative began much earlier in the review process and speaks to the patient engagement we have welcomed long before our draft report release. We disagree that the timing of when survey data becomes available indicates its priority in informing our report. We found it appropriate to release the draft report pending the survey results with full transparency that we believe the findings could help us better quantify certain outcomes, but do not believe the lack of inclusion invalidates our draft conclusions.***
9.	We are also a bit concerned about the methodology of the survey since we understand that it was conducted using SurveyMonkey where anyone could provide responses rather than using a curated and validated source list for obtaining responses. Please respond as to how the survey's methodology will provide useful, valid and robust insights to ICER and SCD stakeholders.	***We agree that the methodology for conducting the survey has limitations. Our collaboration with Sick Cells allowed us to reach a large (convenience) sample of patients and caregivers who were willing and able to participate in the online survey (a total of 454 responses were used in the analysis). This survey will allow us to have estimates for the economic and health impacts of sickle cell disease that are not available elsewhere, such as lost work and productivity, frequency and duration of pain crises, and out of pocket costs of managing the disease. We acknowledge the limitations of the approach in the report and suggest that certain estimates be interpreted with caution.***
10.	Similarly, we question to rush to release the draft evidence report rather than wait until the Budget Impact Analysis (BIA) is finished and available for comment. Presenting the draft report without the BIA precludes public comment and input. We did not see changes to the presentation of the BIA in either the proposed or final updates to ICER's 2020-2023 value framework documents. Will ICER's new standard operating procedure be to NOT include a BIA in draft	***ICER's standard process of including budget impact analysis in draft reports has not changed. The budget impact analysis was not included in this draft report due to time constraints.***

	evidence reports? Does ICER believe that public comment on their BIA is not important or relevant? Given that decisions about coverage and benefits are not made until the middle of the year – or later – for the following year, we do not understand the need to produce the final report by mid-April when a month or two later would provide more useful information to the stakeholders ICER is seeking to influence, e.g., payers planning their next year's formulary structure and access protocols and premiums. Please explain and justify not including the BIA in the draft report and declare what the policy will be moving forward.	
11.	Assumptions While the population of people in the U.S. with SCD are mostly covered by Medicaid and Medicare we are concerned about the use of the Truven database since it is almost entirely commercial claims. And further, it was reported at the 2017 American Society of Hematology Annual Meeting that "Patients with sickle cell disease (SCD) who are insured through Medicaid used hematology care services at a far lower rate than commercially insured patients." And that "Medicaid patients also exhibited greater emergency department (ED) use and lower compliance with hydroxyurea (HU) treatment." Therefore, please explain how the use of a commercial database to model SCD patients care and utilization makes sense and does not invalidate the draft report's conclusions – or at least make them highly suspect as to their magnitude and accuracy.	***When possible inputs for the economic model were taken directly from clinical trials and from published literature on Medicaid and Medicare patients with SCD. When this information was not available, we undertook a study to generate new evidence that could be used in our model. Although the majority of patients in the study received their health care through commercial insurers, the study captured over a third of all patients in the US with SCD. Results from this study were further augmented through partnership with Sick Cells to ask patients and their families about healthcare utilization and costs.***
12.	Additional Points Given that the three new treatment options for SCD have different MOAs – and it is very possible that some people with SCD will benefit from simultaneously using more than one of them – we appreciated ICER including in its disclaimer on page iii that "data inputs to ICER models often come from clinical trials; patients in these trials and provider prescribing patterns may differ in real-world practice settings." We appreciate ICER noting that treatment for SCD in the U.S. is "highly variable," but we would be remiss if we didn't note that this is true for most diseases in the U.S. Therefore, stating that the variability of care for people with SCD "represents a failure of the US health care system" is too myopic because that variability - and this type of "failure" is a systemic situation in U.S. health care rather than a particular problem with SCD. For example, one article found that the consequences of that dysfunction are that 14-16% of health care spending in the U.S. may be directed towards such variability in care that is inappropriate or not useful.	***Thank you for your comment.***
13.	The final report should talk about geographic differences in SCD prevalence across the U.S. since this may be important both for costs and modeling purposes, as well as informing different stakeholders – including regional and local payers.	***We agree that SCD prevalence differs by geographic region. The report chapter on Budget Impact allows decision makers to understand the impact of prevalence on overall costs under different scenarios.***
14.	On page 16, we would suggest editing the statement "ICER now includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets," by inserting the word "fixed" before "health care budgets" since if such budgets are not fixed or predetermined – such as with the U.S. Veterans Health Administration, – then the concept of headroom is inconsistent, e.g., for entitlement programs such as Medicare or Medicaid there is no fixed annual budget, so spending literally cannot run out of headroom.	***Budgets are finite whether they are fixed or not, so reductions in wasteful spending will free up additional funding for other spending in either case.***
15.	In the Patient Perspectives section there are no attributions for the quotations. While we recognize that identifying the individuals who	***We have attributed the quotes to the perspectives they represent (e.g., "Patient living***

	provided those quotes may be inappropriate, we also strongly believe that some indication of the type of person and source of the quote would make them much more meaningful, and add to the transparency and validity of ICER's efforts. For example, we think three pieces of information would be appropriate: o Identifying the quote as coming from a person with SCD, a caregiver, or a clinician; o Their age (or age range), age of the person with SCD they are a caregiver for, or for clinicians their practice setting; and o Source of the quotation, e.g., focus group, public meeting comment, letter/email, personal conversation or similar communication directly to ICER.	***with SCD") and described the source of these quotes in the paragraph that delineates our methods for learning about patient and caregiver perspectives.***
16.	Page 17 – "People with SCD often end up on formal disability programs." This needs to be defined, since we are unaware of what would qualify as an "informal" disability program. We recommend this sentence be more specific, and include data and examples of disability programs.	***Thank you for your comment.***
17.	Conclusions & Recommendations While we recognize the draft report's thoughtful discussion about the severity of SCD for patients and caregivers, and the general undertreatment of people with SCD, Patients Rising Now believes that ICER's Draft Report on the new SCD treatments is incomplete by ICER's own standards, e.g., the survey of patients and caregivers is not complete, and the Budget Impact Analysis is missing. Therefore, the draft report should be reissued when complete. Only then can patient and caregiver comments and perspectives be appropriate included in the process. Just like the clinical dictum that the quality of care should not be sacrificed for speed (except maybe in some emergency situations), we strongly urge ICER to not diminish the validity of its attempted analysis and recommendations to fit an arbitrary and unnecessarily rapid timetable.	***The report will be reissued with the budget impact analysis and survey results on March 12, 2020. A final report will be published April 16, 2020. ICER appreciates stakeholders' continued engagement with the review and looks forward to their participation in the public meeting.***
Sickle Cell Disease Association of America, Michigan Chapter		
1.	I am writing to express our concerns regarding the potential negative impact your "Sickle Cell Disease: Draft Evidence Report" could have on the 2,800 individuals living with sickle cell in our state and across the country. It in effect places a dollar value on the quality of life of our patients. While the report places little value on the difference of one day's hospitalization, our organization represents a community of patients who would treasure one less day for each hospital stay – because a year with sickle cell often results in multiple hospitalizations. Medications that can reduce this burden – in cost, job and educational time lost, family disruption, and other life disruptions – would be invaluable.	***Thank you for your comment. We agree that multiple hospitalizations, educational time lost, job time lost, among other things are important considerations and have included those in our model. But no drug or other health care treatment can be "invaluable" if that means the drug maker can charge ANY price for it. That only leads to the kind of cost pressures that create major problems for Sickle Cell patients and all others. We hope to provide a way to think about a "fair" price that can make sure that drugs are fairly rewarded for their contributions to improving health without causing greater harm than good by contributing to health care costs that are unsustainable for many American families.***
2.	The hallmark of SCD is unpredictable, indescribable pain. Approximately 30% of adults living with SCD have pain every day requiring chronic opioid therapy to maintain any semblance of a productive and meaningful life. In spite of this, when patients present to the emergency room they are frequently perceived as drug seeking. They also experience longer wait times for pain medication than cancer patients. The current opioid crisis has increased the barriers to access much-needed pain medication producing yet another hurdle in	***Thank you for your comment. Our report attempts to discuss many of the systemic issues faced by people with sickle cell disease, including inequity and health care disparities, and points out that decision-makers may give additional weight to treatments that will help reduce the stigma associated with the need for opioids.***

	our patients' struggle to battle this illness that can have a tremendous negative impact on every aspect of their lives. On behalf of the thousands of individuals and families we represent, we urge you to consider the broad-ranging immeasurable impact of each healthy day an individual with sickle cell disease is able to add to his or her community. These days add up to far more than the limited life extension your report cites.	
Supporters of Families with Sickle Cell Disease		
1.	As you stated repeatedly in your report , SCD is a multi-faceted condition that can cause extreme hardships on patients and their families. We at SFWSCD , bear witness to these hardships daily. We see how SCD's impacts on patients vary dramatically from person to person n but that they have multiple periods of severe pain and other complications in common. We see things to varying degrees that individuals and families face , thing is like a life with unce1tain length; lowered educational levels, diminished economy opportunity ; periods of depression and hopeless ness; and so many other is use that have a negative effect on the quality of life . The therapies have been the years in the making, and just like other Orphan Drugs, the potential for transformative life is what our community deserves. We are afraid that, after reviewing the report , payors whose only interest is in economics will likely be persuaded to be reluctant to cover these therapies and /or refuse to cover them altogether.	***Thank you for your comment.***
2.	Your report summarizes that crizanlizumab (Adakveo) has the potential to extend life by 2.4 years, that voxelotor (Oxbryta) could extend life by 2. 1 years and the L-glutamine (Endari) might extend life by approximately I year. We think the answer is that the value is immeasurably higher than any one person or any one scientific analysis ca n quantify. We believe any improvement in care and each gai n in life quality , no matter how incremental they may be, is of significant value to every person and their family impacted by SCD. As a point of reference, I am a parent and a social worker of a child diagnosed with sickle cell disease at 2 months of age. Our family emotional wellbeing has varied from being scared, fee ling isolated, exasperated and misunderstood. Living with an expiration date over your loved one' s life is extremely difficult, frustrating, and overwhelming. I lost my career when our so n was born, and our entire life changed. The sick le cell diagnosis changed the co re of our family and how we operate. Currently, our child requires oxygen daily and sufferers from constant hypoxia that is impacting education achievement, which has the long- term impact of affecting his income potential. Until these drugs, I not only wondered, but mulled over, how I would help him navigate his educational journey and what that would look like. I personally, am excited about the new therapies and the many new possibilities that life now can hold for him.	***Thank you for sharing your story with us. It helps us understand some of the important ways sickle cell disease has impacted your child's life and your family's life.***
3.	That is why we urge you to more strongly consider the unmeasured costs of SCD before releasing your evidence report in April. At the very least, we urge you to more strongly emphasize the significant, immeasurable value of even small improvements in life expectancy, family system and societal benefit and patient life quality	***Our goal with comparative clinical and cost effectiveness evaluations is to encourage pricing of new drugs to be in line with the clinical benefit they deliver. This improves patients access both to new therapies today and makes it possible for the healthcare system to afford and make available new therapies in the future.***
Sick Cells		
1.	1. Introduction a. The authors discuss how patients' baseline health and usual care	***When reviewing the comparative clinical effectiveness, we used the same definition of***

	vary considerably. Thank you for calling this out. Please discuss the implications this has on the analysis included in the report. The comparator is listed as "optimal usual care" however it is not clear how ICER reached a definition of usual care given this variation.	***"usual care" as the clinical trials. After listening to many patients and clinicians we realized that "usual care" in the clinical trials was better than what was happening in the real world. This was further confirmed by what we saw in the real world data from MarketScan. As a result, we labeled this "optimal clinical care" because it didn't reflect what was happening in the real world. For the comparative cost effectiveness section, we chose to use "usual care". This means that in our model we more accurately captured what most patients experience in the real world and not in a clinical trial. The result is that is makes all three therapies look more cost effective in the real world than under clinical trial conditions.***
2.	More information is needed in the background section regarding current treatments. Please discuss which patients the medications are recommended for, as the eligibility may be limited. Additionally, provide details regarding the undesirable side effects of each treatment.	***This information is covered in Section 4.***
3.	Table 1.1 Please provide greater detail on WAC and cost per year.	***We have added additional detail on the source of these costs.***
4.	Include definition for "optimal usual care" utilized as a comparator.	***See previous response.***
5.	Include identification of data measures and data sources utilized for each outcome. For example, quality of life is listed as an acute outcome, however the quantitative vs. qualitative quality of life improvement is an ongoing tension between the patient perspective and the health economics perspective. Please provide greater detail on the definition and measurements used to capture quality of life as an acute outcome.	***Please see references for tables in Section 5.***
6.	Please provide citations for how ICER has defined chronic and acute health conditions.	***Acute means occurring in the short term and resolving in the short term and chronic means once something occurs it continues over time.***
7.	Patient Perspectives We acknowledge and thank the organization for seeking input from patients and patient advocacy organizations to gather the patient perspective on this devastating disease. Please provide specifics on how this information contributes to other sections of the report, including the base-case model. It is not clear how this section has impacted the specifics of the report.	***The patient perspective has influenced almost every section of this report. It helped us identify patient important outcomes, gaps between care of patients in the real world and those in clinical trials, the impact of SCD outside of clinical manifestations, etc. It also provided direct inputs into the economic model. As one example in our economic model we used specific information about missed school and work to better capture the impact of SCD and the potential impact treatments could have.***
8.	We recommend discussing your methods for capturing the patient perspective. Include citation statements where appropriate. For example, the quotes should be attributed to individuals.	***We have attributed the quotes to the perspectives they represent (e.g., "Patient living with SCD") and described the source of these quotes in the paragraph that delineates our methods for learning about patient and caregiver perspectives.***
9.	We appreciate the documentation of racism faced by this community, however, the connection of lack of resources and patient experience to racism is unclear. Please provide citations.	***Racial bias negatively affects the allocation of resources for research and delivery of health care. We have added additional citations to this section to support these statements.***

10.	The "one size fits all" policy for acute pain management is not necessarily a hospital issue. Many states have passed laws on the number of days opioids can be prescribed for acute, opioid naive patients.	***Thank you. We have expanded this statement in the report to also capture state laws and payer coverage policies.***
11.	Summary of Coverage Policies and Clinical Guidelines The authors mention reviewing insurance policies from specific states. It is unclear why these states were selected. The majority of patients with SCD live in other geographic areas not covered by these state-specific insurance policies.	***Given that this report is developed for deliberation by ICER's New England CEPAC Program, the objective of Section 3.1 is to provide a high-level overview of commercial coverage policies nationwide as well as highlight a few public payers representative of the New England area. Section 3.1 is not intended to be an exhaustive summary of every private and public policy for SCD treatments in the United States. We have, however, updated Section 3.1 to now include coverage information for Florida and Texas - states recommended by stakeholders to include due to higher SCD population - when policies were publicly available.***
12.	Comparative Clinical Effectiveness We appreciate the attention to the limitations of RCT inclusion criteria, including the lack of representation from pediatric populations. Please discuss how this impacts ICER's ability to accurately measure benefit for the defined population of patients two years of age and older with sickle cell disease. b. In the conclusion section of each treatment, please footnote the data source for quality of life. Please provide details on the measures and methods used to collect quality of life data, noting if any other sources or real-world data was considered.	***We have performed cost-effectiveness analyses for each product beginning at the lowest age for which the product is labeled and included these results under scenario analyses. Inputs into the model along with references are listed in tables in Section 5.***
13.	Long-Term Cost Effectiveness We recommend for ICER to develop an equity-sensitive framework for diseases that face increased discrimination and stigma, like sickle cell disease. Anticipated equity effects of this review require adaptation of the usual review processes. Quality-adjusted life years fails to capture a wide variety of other benefits such as person's return to economic productivity, school performance, and ability to function as a caregiver for SCD patients. We recommend using a modified equity-sensitive framework to include these factors in the base case analysis.	***We have included societal impacts of sickle cell disease and these treatments as a co-base case in the current report, including productivity and other indirect costs. We have also added a section to the cost-effectiveness section discussing disparities in life expectancy and treatment for the sickle cell disease population, and the potential impact of these treatments.***
14.	ICER extracted data from Medicare and Commercial claims, however Medicaid is a more common payment source among SCD patients. We recommend utilizing Medicaid data for a more accurate representation of the population.	***Data from Medicaid were not available.***
15.	Prevalence estimates reported by Shah et al. 2019 are based on July 01, 2009 and 31 Dec 2012 data. It is unclear how accurately these prevalence estimates reflect the current period with regards to the acute chest syndrome, stroke, and pulmonary hypertension. Similarly, Van Tuijn et al. 2010 uses dated data to estimate the prevalence. We recommend using updated data sources for these prevalence estimates.	***Our estimates for prevalence do not come from these sources, but from Aetion claims data and CMS reports.***
16.	We have identified several concerns related to utility values used in the report: Several utility values used in this report are cited from U.K. studies, such as Anie et al., 2012. These utility measurements are inappropriate to be utilized in this assessment, given the differences between health care, health care systems, and the impacts of race and ethnicity in the	***A systematic literature review was undertaken to investigate data on health-related quality of life for patients with SCD. Much of the literature was collected on patients from the United Kingdom (UK). Where possible values from the US were prioritized for use 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. Given the role of patient utility as a key determinant of value in this model, this is a major concern and limitation. ICER inadequately addresses this uncertainty in the draft report. ii. ICER model input 0.7 utility for uncomplicated SCD patients; however, the Anie utility function is 0.81. Please explain the rationale for using the 0.7 utility function. iii. Anie et al., 2012, estimates "SCD without pain" one week after hospital discharge. These measurements do not accurately reflect the optimal physical, mental, and social functioning associated with SCD patients without pain. Please include utility measures that can more accurately represent the experience of patients without pain. iv. Additionally, Anie et al., 2012, estimates the utility function of patients upon hospital admission from pain crisis. In reality, patients often manage pain in outpatient settings, emergency rooms, or at home. Patients may only be admitted for extreme pain crises. Please include utility measures that can more accurately represent the experience of patients with acute pain crises. v. ICER should assess if utility functions can be derived from the Sick Cells "My Life with Sickle Cell Disease" survey data.	***model; however, US and UK values were generally similar. We now use a value of 0.80 for uncomplicated SCD with minimal pain, based on Anie et al., the best available data we could find for this input.***
17.	We have identified several concerns related to cost estimates: SCD patients experience multidimensional pain, including emotional stress and mood changes. It is unclear if multidimensional pain and the severities of each pain type are accounted for in cost estimates. ICER should review the indirect costs obtained from the Sick Cells survey and consider if the data are appropriate for including in the model. iii. ICER used average cost from Market Scan (non-representative for SCD patients given the use of Medicare and Commercial claims) instead of individual cost data. Majority of the SCD patients have complicated treatment history and typically have comorbidities; treatment is tailored to each patient. So, without accounting for other factors such as indirect costs, the calculated average treatment cost does not reflect the true patient costs.	***The health-related quality of life measures used in the model have domains for pain, anxiety, depression, ability to perform regular activities, etc. The indirect costs collected by Sick Cells have been incorporated into the societal perspective analysis. Similar to the results from the clinical trial, the cohort model represents the average SCD patient and therefore average cost estimates are most appropriate for this model. Costs are varied in sensitivity analyses.***
18.	ICER should include scenario analysis to assess drug price changes when patent protected drugs expire.	***Consistent with best practice at international HTA agencies and with the great preponderance of academic work, ICER's cost-effectiveness analyses do not routinely make estimates of price changes across comparator treatments linked to patent and exclusivity time horizons, given the unpredictability of these changes in the US health care market.***
19.	ICER should consider using Cost Effective Analysis or try using some value of medical innovation beyond QALY. At this moment QALY is missing the value of innovation.	***Along with cost per QALY, our report includes estimates of cost per life-year and cost per equal-value life-year gained, as well as estimates of clinical events avoided through treatment. Consistent with international HTA best practice we do not seek to create a quantitative "bonus" for innovativeness given the opportunity cost concerns and the obvious uncertainty of which treatments will or won't have spillover effects in other disease areas.***
20.	ICER's scenario analysis shows that discount rate has major impact on patient cost. Changing the discount rate to 1.5% will increase the drug price by more than 20%, meaning the model is considerably impacted	***The use of a 3% discount rate in the US as standard for both costs and outcomes are based on estimates of the real consumption rate of***

	by the discount rate change. Provide justification for the discount rate included in this analysis.	***interest and data on real economic growth, which are thought to reflect the social rate of time preference. Discounting has been confirmed by the Second Panel on Cost-Effectiveness in Health and Medicine as a uniform discount rate of 3% applied to both costs and benefits.***
21.	ICER reports "Patients with SCD on optimal usual care are predicted to live to 45 years old, which when discounted at 3% per year equates to approximately 15 additional life-years, 8 additional evLYG, and 8 additional QALYs. " Is this distribution similar in other populations? Please explain in more detail and add relevant citations.	***Patients are expected to live to 45 from 24 which is an additional 21 years. Discounted the additional years lived is 15. This is a mathematical result that 21 years discounted by 3% is 15.8 years.***
22.	Table 5.36: The table shows the Medicare population reports higher prevalence of pHTN, HF, and CKD for ages 18-45 as compared to the prevalence of age 46 and over predicted by model. Please explain how the model accounts for these differences.	***The model incorporates many different data points from many different sources. These many data points all have different effects on the prevalence of disease. The model is calibrated to predict prevalence similar to RWE, but is not exact. This is tested in sensitivity analysis which shows that decreasing risks of disease have little effect on the ICERs.***
23.	Baseline prevalence rate over-reported such as pHTN: The model assumes a high prevalence of organ damage at young age. Please justify the rationale for the high prevalence for organ damage.	***See previous response.***
24.	ICER is potentially over estimating mortality. Patients have mortality risk assigned to each comorbidity thus potentially double counts the mortality risk. ICER should consider methods used by Krueger et al. 2013.	***The baseline mortality rate is adjusted to avoid double counting.***
25.	Potential Other Benefits and Contextual Considerations ICER mentions the impact of racism and bias but does not say how the model accounts for these factors. Are the contextual considerations in section 6.2 reflected in ICER's decisions on effectiveness of the medications? Please discuss the use of the information in this paragraph.	***The report includes a section discussing the disparity in life expectancy for this population, and the potential for treatment to increase life expectancy. However, it is unclear if or how the availability of these treatments would impact the racism and bias faced by this population. Both the Contextual Considerations and Potential Other Benefits Sections are meant to provide this important context to policy makers.***
Clinical Societies		
American Society of Hematology		
1.	ASH has been engaged throughout ICER's sickle cell disease (SCD) assessment and is still concerned that this review is premature and does not take into account extenuating circumstances. The Society understands that it typical for ICER to review not-yet-approved or just recently approved drugs. ASH, however, has tried to stress why the SCD community is unique and outline our concerns about the potential adverse impact ICER's assessment could have on recent and future progress of new therapies – the SCD community is on the cusp of benefiting from new, potentially life-changing, treatments and cannot afford a setback. This remains a concern for the Society and is outlined in the comments below.	***As noted, ICER tries to evaluate therapies around the time of FDA approval because that is when clinicians and patients need to make decisions using the best available evidence, and is equally the time when insurers make coverage decisions and drug makers set their price. We hope that ASH shares our belief that a report that takes far more note of the potential other benefits and contextual considerations in this area than payers will normally be able to do on their own does not threaten a "setback" for the SCD community.***
2.	The studies used for ICER's assessment – the SUSTAIN trial for crizanlizumab and the HOPE trial for voxelotor – represent only one trial on acute use for each of these treatments. While this is the evidence that is currently available, it may not be representative of what the research and medical community may learn about these	***We agree that there is limited data on the impact of these new therapies on quality of life as well as acute and chronic conditions associated with Sickle Cell Disease. Working with clinical experts we have developed the***

	drugs in the future. ASH members believe these treatments will have positive long-term impacts on the quality of life for individuals living with SCD that likely will also impact end organ disease outcomes and survival for patients. Because these drugs were just recently approved, these impacts have not yet been realized. Real world patient experience is difficult to demonstrate in a clinical trial and to account for in models. This is especially true in models where the drug has never been used in long term settings, for any disease, from which to extrapolate or estimate.	***most comprehensive model of SCD treatment effect that has ever existed, and have generally taken the most favorable assumptions at every point in which there is significant uncertainty.***
3.	Patient Perspectives ASH would like to thank ICER for the time and dedication the Institute put into understanding the perspectives of SCD patients. The Society appreciates that the report captures that "the way patients with SCD have been treated in the US is a tragedy that has extended over many decades," that "patients and their families have experienced neglect, racism, and total disregard," and that the "overall 'system' of health insurance and care has betrayed the SCD community." These powerful statements touch on the unfortunate reality of what hematologists see every day when treating individuals with SCD. While comprehensive, the patient perspectives section could go even further by capturing that some individuals with SCD experience post-traumatic stress disorder related to severe episodes of illness. Furthermore, many adult SCD patients often need to bring an advocate for emergency care to increase the chance of receiving appropriate treatment for pain. The SCD patient population faces varied and severe challenges that are extremely difficult to capture in a report. We believe these issues should be strongly considered as factors that "reduce important health disparities" in a vulnerable population experiencing "particularly high severity in terms of impact on length of life and/or quality of life" and a "high lifetime burden of illness", as listed in Table 6.1. Potential Other Benefits or Contextual Considerations.	***Thank you for these comments. The voting members of the CEPAC will see them. We have also addressed these considerations in the Patient Perspectives Chapter and Potential Other Benefits and Contextual Considerations Chapter.***
4.	Interpretation of Clinical Data ICER's report states that although crizanlizumab reduced pain crises, it is unclear if the reduction seen is enough to produce a meaningful improvement in quality of life for patients. While one pain event might seem insignificant in terms of an assessment of clinical or cost effectiveness, it is likely very significant to the individual experiencing these severe pain crises and extends beyond the two weeks of decreased utility included in the model to include school, work and family disruption. As stated above, no report or model can fully capture the extreme challenges of living with SCD nor the impacts that a particular treatment might have on an individual patient, let alone the community of patients with SCD who suffer from severe pain. ASH looks forward to seeing the results of the patient and caregiver survey and hopes to have an opportunity to review the resulting changes to the draft report in advance of the public meeting. For example, the crizanlizumab study showed that 35.82% of participants in the treatment arm vs. 16.92% in the placebo arm (p=0.013) experienced zero pain crises (Table 4.2). The potential to eliminate pain crises would have profound effects on the lived experience of patients with SCD in ways that are not captured in your analysis but hopefully will be revealed in your survey.	***We did not intend to undermine the importance of a reduction in pain crises and have modified that statement in the report. In addition, we have added a discussion to Chapter 4, Uncertainty and Controversies, about uncertainties related to how well current quality of life metrics can capture changes in quality of life for a patient living with SCD.***
5.	Potential Other Benefits ICER's report includes an opportunity to provide information on	***Thank you for your suggestion. It will be added to the Evidence Report.***

	potential other benefits offered by the interventions to the patient, caregiver, delivery system, other patients, or the public that may not have been considered as part of the evidence on comparative clinical effectiveness or cost-effectiveness. For this section, ASH would again like to highlight the potential positive long-term impacts these treatments could have on the quality of life and on end organ disease for individuals living with SCD. It would be impossible to fully consider these benefits as part of the evidence on comparative clinical effectiveness because these drugs were too recently approved, and these potential long-term impacts are not yet realized. As noted in your report, all treatments evaluated are projected to increase life expectancy, which is an especially important goal in a population whose life expectancy is 20-30 years less than the U.S. general population.	
6.	An additional potential other benefit for consideration is the increased interaction with health care providers as a result of crizanlizumab being an infused treatment every four weeks. This increased interaction may permit additional services to be delivered at these scheduled visits, further improving patient outcomes. ASH believes that all of these new treatments have the potential to improve connections between this vulnerable patient population and health care providers.	***We agree with your comment and will add this important potential other benefit to our Evidence Report.***
Other		
William Gerber		
1.	Item 1: Page 37: "At baseline, patient characteristics were balanced across intervention arms". This is highly questionable. As you can see in Table 1 of Vichinsky E. et al, 2019, A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease, homozygous hemoglobin S (HbSS) comprised 80% in the placebo arm, and 68% in the 1500 mg voxelotor arm. Numerous published articles describe HbSS as having the worst prognosis of all genotypes. Note Vichinsky et al. does not use the term "balanced", but rather "generally well balanced". The 12% HbSS imbalance may have affected some of the results reported in the study, especially those that did not show statistically significant differences but only "positive trends", such as vaso-occlusive crises (VOC) (discussed in Item 2)	***We have revised the language in the "Key Studies of Voxelotor" section to reflect these differences.***
2.	Item 2: Table 5.12 Treatment Effects ICER made an unusual decision to include a non-statistically-significant relative pain score of 0.868 as a legitimate positive "treatment effect" favoring voxelotor. Furthermore, despite a significant dose-response relating to Hemoglobin (Hb) in the 1500 mg versus 900 mg arms, there was no dose-response relating to VOCs. The 900 mg arm had per-person-year pain crises of 2.76, or 0.865 relative to placebo, versus a slightly worse 2.77 for the higher 1500 mg group, 0.868 relative to placebo. What is the rationale is there to view VOC difference between the 1500 mg and placebo arms as other than a statistical artifact? Also, as mentioned above, the 12% imbalance in HbSS genotype should be considered when evaluating treatment effect "positive trends". Should the lack of statistically significant and dose-response at least be highlighted, with a rationale for using 0.868 given?	***The non-statistically significant effect on VOC was included in the model in an attempt to be optimistic towards the new treatments.***
3.	Item 3: Difference between hemoglobin and "hemoglobin-voxelotor complex". Voxelotor has been described as binding to the N-terminus of Hb alpha chain, creating conformation changes in Hb. It is unclear whether "hemoglobin" and "hemoglobin-voxelotor complex" should be used interchangeably. It is unclear to me how literature supporting the	***We are in agreement. This will be noted in our Evidence Report.***

	benefits of higher hemoglobin on the acute and chronic conditions cited in Table 5.13 should be extrapolated to hemoglobin-voxelotor complex formed by treatment with voxelotor. Global Blood Therapeutics did not prove that Hb supplementation with hemoglobin-voxelotor complex has the same beneficial effects as supplementation with normal hemoglobin. Should this be highlighted and how should the potential drug effects shown in Table 5.14 be interpreted with regard to voxelotor?	
4.	A particular concern is the assumption by those developing cost per QALY lifetime models that the EQ-5D has interval measurement properties. It does not. The EQ-5D has only ordinal properties, it is a manifest scale, and should not be used to construct QALYs. Unfortunately, apart from the lack of scientific merit in constricting lifetime imaginary models, the misapplication of the EQ-3L utilities means that your reference case model collapses. We note that Drummond et al in the last edition of their textbook maintain that the EQ-5D has interval properties. This is incorrect; their arguments are confused. I suggest the following references may assist you in exploring this question. The issue is that the EQ-5D was not designed to have interval properties. If you want to attempt to demonstrate it has (ex post facto) then you need to show that for each disease state application (unidimensional).	***We (and most health economists) have the understanding that the EQ-5D (and other multi-attribute utility instruments) do have interval-level properties. The EQ-5D value sets are based on time trade-off assessments (which are interval level), with preference weights assigned to different attributes. We fail to see why this should be considered as an ordinal (ranked) scale.***
Paul Langley		
1.	There are a large number of potentially competing models for the application of a reference case framework. Why did ICER choose this particular model framework (Section 5.1)? Outcomes (1)ICER points out (Section 5.1) that SCD 'has a large impact on patient's psychosocial wellbeing'. If this is the case, why did ICER chose to model with the EQ-5D-3L system which only captures five symptoms with 3 response levels? Outcomes (2)Why did ICER utilize the EQ-5D-3L system when there are others to choose from, including the EQ-5D-5L (introduced in 2009) which is considered to be more sensitive in capturing responses? Outcomes (3)Given the number of alternative generic utility instruments why did not ICER caution readers that choice of an alternative system (e.g., EQ-5D-5L) could lead to different QALY measures?	***The rationale for the model's structure and assumptions are provided in the report text describing the model. The EQ-5D is a widely-used generic QoL/utility measure, and the values used in the model were subjected to sensitivity analyses. We did not find suitable EQ-5D-5L value sets to use for this population. We have noted in the limitations section of the report that different instruments could lead to different QALY estimates.***
2.	In early 2019 ISPOR published a good practice for outcomes research task force report (Brazier et al, Value Health 2019;22:367-75) for the identification, review and use of health state utilities for cost-effectiveness models. ICER appears to have ignored this practice recommendation. Why? Where is ICER's systematic review (pg. 70)? There is no reference to the Brazier paper.	***ICER conducts extensive literature searches for its reviews of clinical effectiveness and cost-effectiveness model inputs, including utility values.***
3.	In respect of 5 (above) would ICER consider withdrawing its evidence report until a systematic review is presented to justify it choice of the EQ-5D-3L? If not, why not?	***After review of the published utility values for this population, we selected what we believe to be the inputs best fit for the model.***
4.	Given ICER's choice of utilities for constructing QALYs, could ICER demonstrate from one or more empirical assessments that the EQ-5D-3L has interval fundamental measurement properties for the target SCD hypothetical population in its reference case modeling?	***Please see the comment regarding the EQ-5D's properties above.***
5.	In respect of 7 (above), if there is no evidence would it be reasonable to assume that ICER has simply assumed that the EQ-5D-3L for the hypothetical SCD has interval measurement properties? 1. Outcomes (8) If the EQ-5D-3L for the target SCD population has only ordinal measurement properties, how would ICER justify constructing QALYs?	***Please see the comment regarding the EQ-5D's properties above.***
6.	In Table 5.16 presents utility estimates 'by assumption'. How does ICER justify this? Are they assumed to have interval measurement	***Where SCD-specific utility data were not available, assumptions were made that favored***

	properties? 1. Outcomes (10) In the report on oral semaglutide ICER introduced two separate utility systems (EQ-5D-3L and HUI Mk2) into its model? How can ICER justify this when the systems are quite different?	***the treatments. In all cases, utility values are subjected to sensitivity analyses over plausible ranges.***
7.	1. Imaginary Worlds Is the reference case imaginary lifetime model intended to generate credible, evaluable and replicable claims for cost-effectiveness? If not, why not? 2.How much credibility should be attached to the ICER model when it is only one of many that could create imaginary claims in SCD for the products assessed? What sets the ICER model apart from others?	***Descriptive and predictive models are a mainstay of economic analyses, as well as most other scientific disciplines. We use transparent models that follow standard practices and are subjected to multiple scenario and sensitivity analyses.***
8.	1. ISPOR: Approximate Information In the 2018 ISPOR task force report on health Economics (Neumann et al, Value Health 2018;21:119-25) it is determined that economic evaluations are intended, not to test hypotheses, but to inform decision makers of the approximate value of interventions in terms of incremental cost-per-QALYs gained. Does ICER subscribe to this view? 2. ICER: Approximate Information In respect of 14 (above) how would ICER define 'approximate value'? 1. ICER Approximate Information How would ICER differentiate 'approximate information' from 'approximate disinformation'? 2. ICER Approximate Information Where different utilities and model structures are presented in SCD lifetime modeled claims, how would ICER propose that their modeled 'approximate information' is more 'approximate' than other modeled claims for 'approximate information'?	***ICER's value framework recognizes that decisions need to be made using evidence available at the time, no matter how approximate or uncertain. Our reports discuss in detail the variance and uncertainty around the available evidence for the clinical effectiveness of treatments. Our economic analyses explore uncertainty via scenario and sensitivity analyses, including probabilistic sensitivity analyses over plausible ranges of values.***
9.	1. Lifetime Model The ICER SCD model takes a lifetime perspective? How, therefore, are we to interpret the 'assumptions' driving this lifetime construct? Are they a 'realistic guess' or what?	***The report clearly states the assumptions used for the lifetime horizon model, along with the rationale.***
10.	1. Model Assumptions ICER's models look to a future imaginary world for SCD intervention that extend decades into the future for a hypothetical SCD population. This relies on assumptions that have held in the past (from the literature), and are presumably assumed to hold into the future. Given Hume's induction problem, how does ICER justify a model built on assumptions?	***As pointed out above, descriptive and predictive models are used throughout modern scientific analysis.***
11.	1. Rasch Measurement It has been recognized since the 1960s (and in in health technology assessment since the 1990s) that if we are to capture the patient voice in therapy assessments, we require a needs based QoL instrument to capture therapy impacts with interval measurement properties. Why has ICER continued to apply generic measures of HRQoL defended by what many see as a bogus population perspective argument? Could ICER provide their case for non-patient centric HRQoL measures?	***Please see the comment regarding the EQ-5D's properties above.***
12.	1. Hypothetical Population What is the case for modeling to create non-evaluable claims based on a hypothetical SCD population? Why was this particular population selected for creating the ICER imaginary lifetime SCD world? Does the EQ-5D have unidimensional interval scale properties for the target SCD population?	***The rationale for the population used in the model is described in the report. Please also see the comments regarding modeling and the EQ-5D's properties above.***
13.	1. Multiplicative Assumption In respect of 9 (above), if ICER cannot demonstrate that the EQ-5D-3L has interval properties, rather than ordinal, how does ICER justify the statement that HRQoL is multiplicative (Table 5.4)?	***Please see the comment regarding the EQ-5D's properties above.***
14.	1. Assumptions Why should we' believe' ICER's assumptions as opposed to the assumptions underpinning competitor models? 2. Assumptions Why should treatment effects from clinical trials be transferable to a reference case imaginary world?	***The assumptions used in our models are clearly stated, along with the rationale for each, and are tested in scenario and sensitivity analyses. Please also see the comment regarding analytic modeling above.***

15.	1. Interval Scoring In respect of the utility estimates in Table 5.16. Can ICER show that each of these has interval scoring properties (including the NICE report)? This applies also to the 'calculated' utilities.	***Please see the comment regarding the EQ-5D's properties above.***
16.	1. Validation Why has ICER ignored empirical validation (pg. 75) of claims? 2. Validation In respect of 14 (above). Why has ICER sidestepped the question of empirical validation of the cost-effectiveness claims made in their reference case model? 3. Validation Are any of ICERs claims in SCD capable of empirical assessment?	***The report includes comparisons suggesting that predicted prevalence in the model is very similar to that of the Medicare population in terms of chronic disease prevalence.***
17.	1. Base Case Results Would ICER agree that if it cannot be demonstrated that the utilities for the hypothetical SCD population fail to demonstrate interval properties then the QALY base case results for the SCD products (Table 5.22) are meaningless? [i.e., lifetime QALYs are a mathematically meaningless fabrication]	***Please see the comment regarding the EQ-5D's properties above.***
18.	1. Thresholds Would ICER agree that if it cannot demonstrate the integrity of lifetime cost-per-QALY claims (meeting fundamental measurement standards) then recommendations for pricing and affordability based on such claims are questionable?	***Cost-effectiveness analysis using QALYs are considered the gold standard in the field of health economics. Again, please see the comment regarding the EQ-5D's properties above.***
19.	1. Media Releases Many companies have concerns that the media release ICER's recommendations for price discounting and affordability without detailing the model and its assumptions. Would ICER consider adding the following caution when its reports are released? ICER wishes to emphasize that any conclusions and recommendations made in this report are specific to the model structure and its assumptions devised by ICER. Alternative models could be developed with their own structure and assumptions and come to possibly quite different conclusions and recommendations.	***ICER's reports and other communications always strive to include appropriate details of, and to point out any limitations of, its assessments.***
20.	1. Health Related Quality of Life Construct ICER makes clear (to a certain extent) the difference between health related quality of life (HRQoL) and the broader concept of quality of life (QoL). In adopting the EQ-5D-3L as the utility measures, could ICER make clear as to what is the latent construct (if any) or other construct(s) that ICER is unable to provide this assurance, it should be made quite clear.	***As pointed out above, the EQ-5D has a broad history of use in health technology assessments, as well as an extensive literature on its measurement properties.***