AMERICAN SOCIETY OF HEMATOLOGY
2021 L Street, NW, Suite 900, Washington, DC 20036 ph 202.776.0544 fax 202.776.0545 e-mail ASH@hematology.org

February 20, 2020

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review (ICER)
Two Liberty Square
Boston, MA 02109

Re: ICER's Assessment of Treatments for Sickle Cell Disease

Dr. Pearson,

The American Society of Hematology (ASH) appreciates the opportunity to offer comments in response to the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report: Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value.

ASH represents more than 18,000 clinicians and scientists worldwide who are committed to the study and treatment of blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sickle cell anemia, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy.

ASH 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.

2020-2023 Value Assessment Framework

The Society is aware of ICER's new 2020-2023 Value Assessment Framework, just finalized January 31, 2020. While the document is meant to guide future ICER assessments, ASH believes that reviews, such as the current SCD assessment, should also benefit from many of the changes outlined in this new framework, including the two noted below.

- Augmenting Efforts to Use Real-World Evidence: For drugs that were approved under accelerated approval pathways, ICER will pilot a formal process to update the original assessment after the treatment has been on the market for at least 24 months to explore how best to develop and assess new real-world evidence.

- Creating a New Process for Re-evaluating Evidence: One year after the release of each Final Evidence Report, ICER will formally reassess whether new evidence has emerged that should be included in an update to the report.

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 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.

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.

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.

Potential Other Benefits

ICER's report includes an opportunity to provide information on 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.

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.

Thank you for the opportunity to submit comments. Should you have any questions or if you would like to discuss these comments further, please reach out to Leslie Brady, ASH Policy and Practice Manager, at lbrady@hematology.org or 202-292-0264.

Sincerely,

Stephanie J. Lee, MD, MPH
President