September 20, 2019

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) is pleased to offer comments in response to the Institute for Clinical and Economic Review’s (ICER) Draft Scoping Document on the assessment of the comparative clinical effectiveness and value of crizanlizumab (Novartis) and voxelotor (Global Blood Therapeutics) for the treatment of sickle cell disease (SCD).

ASH feels it is important to reiterate the concerns outlined in our August 27 letter regarding the history of SCD. As mentioned in our first comment letter, SCD was the first ever molecular disorder discovered, with the first case reported in 1846 and the first formal description coming in 1910. The SCD community has long been disenfranchised, and unfortunately, this has led to a lack of therapies and treatments. Additionally, there is a high level of mistrust of the healthcare system amongst this patient population. Currently, however, there is enormous opportunity for new, potentially life-changing treatments.

ICER does not conduct reviews for every approved or yet-to-be-approved therapy and this first review for treatments for SCD is coming at such a significant time in the research and development of new therapies for this disease. ASH is concerned that these factors could make this assessment appear as though SCD drugs are being held to a different standard; thereby, fueling the mistrust of this population and unintentionally, hurting access and future development of new therapies. ASH, the National Institutes of Health, and the Food and Drug Administration (FDA) have invested a great deal of resources to help change this dynamic. Given the number of new treatments in the pipeline, ASH is concerned that ICER’s process could diminish the progress of the last several years. Therefore, the Society hopes that ICER’s process will recognize the overall lack of progress on this disease until recently and the mistrust of the healthcare system felt by the patient population.

If ICER moves forward with this assessment, ASH would like to provide comments specific to the following areas of the Scoping Document:

1. Background
2. Analytic Framework
3. Interventions and Comparators
4. Key Outcomes and Harms
**Background**

ASH noted the following discrepancies in the *Background* section of the Scoping Document:

- There was a marked decrease in mortality in children under five in the US from 1979-2006, not in infants (Page 1).
- L-glutamine (Endari) is also FDA approved as a disease modifying therapy for SCD although the data is limited to sickle cell anemia (Page 2).

**Analytic Framework**

ASH offers the following comments on the Analytic Framework:

- ICER states that the population of focus for this review is children two years of age and older and adults diagnosed with SCD; however, there is no published data on the use of these new therapies in children age two. Crizanlizumab lower age was 16 and voxelotor was 12.¹,²
- As the Institute recognizes, there are a number of different genotypes of SCD and from what we know to date, not all genotypes will be eligible to receive both of the therapies under review. ASH requests that ICER’s model be specific as to which segments of the SCD patient community it will include.

**Interventions and Comparators**

In the Scoping Document, ICER outlines its plan to compare crizanlizumab and voxelotor to “usual care alone,” defined in the document as hydroxyurea (HU) and transfusions. ASH wants to ensure that ICER’s model will take into account that many patients do not receive what the Institute is defining as “usual care.” We strongly encourage the Institute to ensure that its model recognizes that “usual care” is suboptimal and accommodate for the current issues affecting access to “usual care,” as well as anticipate access challenges for the new treatments.

As was expressed on ASH’s Scoping Call with ICER staff, “usual care” is very hard to define for this population. Care is not the same for any two patients with SCD – it may look different for different subtypes or for individuals who have suffered different complications of SCD. Many individuals living with SCD struggle to access care and those who successfully receive care may be hesitant to follow recommended care for a number of reasons. For example, ASH members find that many SCD patients are hesitant about taking HU because of the side effect profile that they find online while doing their own research. There is concern that it is “chemotherapy” and patients fear side effects, such as hair loss. While physicians do their best to dispel these myths, sometimes

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families remain resistant to giving HU to their children. Similar concerns exist in the adult population. Additionally, some individuals cannot tolerate HU and therefore, do not take it.

Key Outcomes and Harms

ASH offers the following comments on the Key Outcomes and Harms:

- The Society would like to expand upon the significance of pain in the lives of individuals with SCD and wants to ensure it is adequately represented in ICER’s model. ASH agrees that pain is a significant part of daily life for individuals with SCD and appreciates that both chronic and acute pain are listed in Table 1 and that a description of SCD pain is included in the Background section. Recurrent severe acute painful crises and chronic daily pain are the most common complications of SCD. Severe acute painful crises often require treatment in the hospital emergency department. In addition, 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. ASH is currently in the process of finalizing five clinical practice guidelines on the management of acute and chronic complications of SCD, and pain is one of the topics addressed. Publication of the new ASH SCD guidelines is anticipated in late 2019 through early 2020.

- Hospitalization is listed under “Key Measures of Clinical Benefit.” The Society recommends including emergency department visits and day hospital visits to this list.

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,

Roy L. Silverstein, MD
President