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Steven D. Pearson, MD, MSc
President
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Two Liberty Square
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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) planned 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 represents over 17,000 clinicians and scientists worldwide, who are committed to the study and treatment of blood and blood-related diseases. As ICER embarks on its SCD review, ASH wishes to caution the Institute that it must understand and respect the history, experience and characteristics of the SCD community. The Society understands ICER's process but wants to stress that scientific discoveries in SCD have finally resulted in the development of many new agents and approaches that could provide meaningful benefits to this extremely vulnerable population and we do not want to see an ICER review harm this progress. The SCD community has often felt disenfranchised and even betrayed by health care systems, so building and maintaining trust is essential if we are to advance new therapeutic opportunities.

**History of Sickle Cell Disease**

SCD is the first ever molecular disorder discovered with the first case reported in 1846 and the first formal description coming in 1910. Yet, advances in treatment have been slow and difficult to implement, especially compared with later discovered molecular diseases – such as cystic fibrosis – where multiple treatments have benefited the patient population. Surprisingly, many very basic scientific processes related to SCD are not well understood and there are only two approved therapies to date. There is enormous opportunity, however, and ASH is excited that the SCD community is on the cusp of benefiting from new, potentially life-changing, treatments. This patient community has waited more than 100 years for these treatment options and the Society wants to see that advances in SCD care and treatment including these promising therapies move forward.

Recognizing the vulnerability and history of discrimination faced by patients living with SCD, in 2015 ASH launched a transformative, multi-faceted, patient-centric initiative to improve outcomes for individuals with SCD, both in the United States and globally, by bringing together stakeholders in the public and private sectors committed to significantly improving the state of SCD worldwide. The focus of the SCD initiative and invested resources has been on improving access to care, improving clinical outcomes through development of evidence-based guidelines describing the appropriate management of acute and chronic complications of SCD, educating hematologists and other health care providers to improve the care of individuals with SCD, supporting research, and addressing global issues, especially related to

newborn screening. ASH and the U.S. Food and Drug Administration hosted a SCD Clinical Endpoints Workshop in October 2018 to discuss opportunities to bring uniformity and standards to existing SCD endpoints, identify gaps, and propose development of new endpoints as a focus for future research. ASH also recently established the ASH Research Collaborative (ASH RC) to advance SCD research through the sharing of data on hematologic conditions and the ASH RC Sickle Cell Disease Clinical Trials Network – a network of collaborating clinical research sites to accelerate and optimize clinical trial research in SCD.

Although the Society has concerns about the potential adverse impact ICER's assessment could have on recent and future progress of new therapies, ASH appreciates the opportunity to provide comments in the following areas:

1. Consideration of use of ICER's value assessment framework for treatments for ultra-rare diseases
2. Exclusion of voxelotor
3. ASH members with expertise in SCD

**Consideration of use of ICER's value assessment framework for treatments for ultra-rare diseases**
For this assessment ASH encourages ICER to consider using the value assessment framework for treatments for ultra-rare diseases. The ultra-rare framework is typically used for treatments impacting 10,000 or fewer individuals, when there is little chance that further expansions of the drug's indication or population would extend it above 20,000 individuals, and when the treatment offers a potential major gain in improved quality and/or length of life. ASH believes the ultra-rare framework is appropriate for assessment of crizanlizumab and voxelotor because of lack of data for this patient population as a whole, as well as the need for ICER's review to include the many other benefits and contextual considerations of these treatments that will affect coverage and funding decisions.

Unfortunately, there is a lack of reliable data for the SCD population. This makes it impossible to know with certainty how many individuals in the United States currently have SCD, where these individuals live, how they are insured, or where they seek medical treatment. Additionally, many times, and as is the case with voxelotor, treatments are only applicable to a certain subset of individuals, who meet specific clinical criteria. Again, due to a lack of data, little is known about the number of individuals with SCD who would meet these criteria; for example, the estimates for the percent of the SCD population eligible for voxeletor range from 10 percent (approximately 10,000 individuals) to as high as 60 percent.

The ultra-rare framework allows for broader consideration of how treatments affect the patient's family, school and community. Due to recurrent severe acute pain episodes, chronic daily pain and the many other complications of SCD, including anemia, acute chest syndrome, and stroke, individuals living with SCD are often unable to maintain a typical lifestyle, leading to missed days of school or work. Furthermore, many, if not most, of this patient population are insured through Medicaid, which includes a limited supply of SCD specialists providing care, limitations on covered services and an increased reliance on emergency department care.

While it is unclear whether voxelotor and crizanlizumab meet the numerical criteria threshold to qualify for the ultra-rare framework, given the significant effects that SCD and these treatments may have on family, educational, and community settings, as well as the broader health care system and public and private payer budgets, we believe that it is appropriate for ICER to use a broader lens in its review.

**Exclusion of voxelotor**
Based on information from ASH clinical experts, the Society believes that the significant differences between voxelotor and crizanlizumab make them inappropriate for comparison in this review. Accordingly, we support the removal of voxelotor from this assessment. Besides having different clinical goals and affecting different patient populations, crizanlizumab and voxelotor also have different mechanisms of action.

Crizanlizumab has been shown to be helpful in preventing vaso-occlusive crises (VOC), which are a common occurrence in individuals with SCD and therefore, will likely be applicable to most SCD patients.

The situation is less clear with voxelotor as there are not yet enough clinical outcomes data. It appears that voxelotor may be helpful for a subset of SCD patients with low hemoglobin/high hemolysis phenotype who do not respond to or do not want to take hydroxyurea.[1] As voxelotor continues through clinical trials, we will obtain more clinical outcome data that will make the benefits more clear.

**ASH Member sickle cell disease experts**
ASH represents over 17,000 clinicians and scientists worldwide. ASH members include clinicians who specialize in treating children and adults with SCD and researchers who investigate the causes and potential treatments of SCD manifestations. ASH members are at the forefront of SCD research and treatment. It is critical that ICER work with SCD experts in completing this assessment and ASH would be happy to identify experts to participate in the ICER process.

Thank you for the opportunity to submit comments. ASH looks forward to remaining engaged as ICER continues with this assessment. 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

[1] Elliott Vichinsky, et.al., A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. The New England Journal of Medicine. 2019;381(6):509-591.