Crizanlizumab and Voxelotor for Sickle Cell Disease: Effectiveness and Value

Draft Background and Scope

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Background

Sickle Cell Disease (SCD) is a broad term referring to a group of inherited disorders carried by the beta (β) allele of the hemoglobin gene (Hb). It is characterized by abnormal hemoglobin polymerization during deoxygenation resulting in sickle shaped erythrocytes (red blood cells [RBCs]). SCD includes the genotypes HbSS, as well as the compound heterozygous genotypes HbSβ^0 thalassemia, HbSC, HbSD, HbSβ$^+$ thalassemia.[1] The genotypes HbSS and HbSβ^0 thalassemia have similar clinical characteristics and together are frequently referred to as sickle cell anemia (SCA). Conversley the heterozygous state with one normal gene and one Hb S gene (HbAS) is the carrier state and is referred to as "sickle cell trait". Sickle cell trait usually does not have clinical manifestations and confers protection against plasmodium falciparum malaria.[2]

Clinical manifestations of SCD derive from at least three different pathophysiologic mechanisms: The loss of deformability of the RBC leading to vascular obstruction and ischemia; a shortened lifespan of the RBC leading to both intravascular and extravascular hemolysis; a sticky RBC surface increasing adherence to the vascular endothelium which can result in vascular obstruction and can contribute to vascular proliferative lesions.[3]

Rates of SCD and sickle cell trait vary considerably by geography with the highest rates found in populations arising from areas where, historically, resistance to plasmodium falciparum malaria conferred a survival advantage.[2] These include equatorial Africa, Brazil, Saudi Arabia and central India. The incidence of SCD is estimated at 300,000 to 400,000 live births globally. In the United States (US), the current best prevalence estimate is approximately 100,000 individuals with SCD, although comprehensive surveillance and reporting is lacking and the true number of cases in the US is unknown.[4]

A marked decrease in mortality in infancy occurred in the US from 1979-2006, presumably due to the implementation of universal newborn screening, penicillin prophylaxis, and the use of conjugated pneumococcal vaccine.[4] During that same time, peak mortality shifted from the middle third decade of life to the late fourth decade of life with the mean age of death being 39 years.[5]

Despite improved survival, life expectancy continues to be 20-30 years less than the US general population.[4]

Recurrent acute pain crises, or vaso-occlusive crises (VOCs) are considered among the most common manifestation of SCD. VOCs are believed to occur when blood flow is obstructed, usually at the level of the small blood vessels resulting in ischemic injury and pain.[3] The management of acute pain crises is extremely important in patients with SCD yet is often misunderstood or inadequately addressed across all healthcare settings.[1]

In addition to VOCs, over time patients experience significant acute and chronic morbidity. Acute complications include serious infections such as meningitis, osteomyelitis, and sepsis, and non-infectious complications such as stroke, renal necrosis, priapism.[6] Acute chest syndrome is a potentially life-threatening complication that can involve chest pain and shortness of breath among other symptoms; some episodes of acute chest syndrome are triggered by infection.[7] Chronic complications can emerge across multiple organs and include neurocognitive impairment, chronic kidney injury, delayed puberty, avascular necrosis, retinopathy, pulmonary hypertension, skin ulcers, and chronic pain.[6] Individuals with SCD face ongoing and evolving lifelong difficulties as a result of their disease. As their bodies grow, develop, and age, new problems can emerge while intermittent and persistent vaso-occlusion/ischemia produce an accumulation of injuries over time.[2] Resultant health care costs are high, with the total health system economic burden of sickle cell disease estimated at $2.98 billion per year in the US with 57% due to inpatient costs, 38% due to outpatient costs, and 5% due to out-of-pocket costs.[8]

At this time, there are only two interventions considered to be disease modifying: chronic transfusion with packed RBCs and hydroxyurea.[1] Chronic transfusion is generally used for primary or secondary stroke prevention; hydroxyurea is used to reduce the number of VOCs in those with frequent or severe crises, and in those with a history of acute chest syndrome or severe anemia.[1] L-glutamine supplementation can also decrease the frequency of VOCs.[9] Acute VOCs may be managed with pain medications including opioids, and may require additional inpatient or outpatient treatments including hydration, transfusion, supplemental oxygen, and a variety of other treatments.[1]

There is clearly a large unmet need for additional treatments for SCD. Crizanlizumab (Novartis), is a humanized monoclonal antibody that binds to P-selectin. It is currently being evaluated by the US Food and Drug Administration (FDA) as prophylactic treatment for VOCs.[10] It is administered intravenously every four weeks. The FDA is expected to issue a decision on approval by January 2020. Voxelotor is an HbS polymerization inhibitor that reversibly binds to hemoglobin to stabilize the oxygenated hemoglobin state, thus shifting the oxyhemoglobin dissocation curve.[11] Voxelotor is currently being evaluated by the FDA as a treatment to increase Hb levels. It is administered

orally and is dosed daily. A rolling New Drug Application for voxelotor is expected to be submitted before the end of 2019, with an anticipated FDA decision between mid to early fall of 2020.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. A final scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

We heard from patients and patient groups about the tremendous burden of SCD due to chronic pain, recurrent acute pain, and accumulated organ damage. Families often had multiple members affected by SCD and described watching parents, children, and siblings suffer and then die at an early age. We heard repeated concerns that doctors and other medical providers are inadequately trained in the management of SCD and fears that even when new treatments become available there will be delays in their availability for patients because of lack of provider knowledge. We also heard that patients routinely face stigma because of a belief that they are "drug seeking", and that this is heightened by racism and bias against the populations of color most affected by SCD. Patients and family members described delays in getting adequate pain medication, inappropriate delays in life-saving interventions in acute care facilities, and how provider concerns about inappropriate opioid use have led to situations where almost anyone involved in a patient's inpatient care can interfere with prescribed access to opioid pain medications. Family members described the burdens of caregiving, including the need to leave the work force to provide care, and also how those with sickle cell trait would choose not to have children to avoid passing on the gene to the next generation. Patients, families, and patient groups described the financial toxicity of treatments for SCD and that many patients are disabled from working. Patients and family members described making decisions to avoid marriage to maintain insurance. Everyone we spoke with expressed excitement at the possibility of new treatments for this severe disease.

Report Aim

This project will evaluate the health and economic outcomes of crizanlizumab and voxelotor for sickle cell disease. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

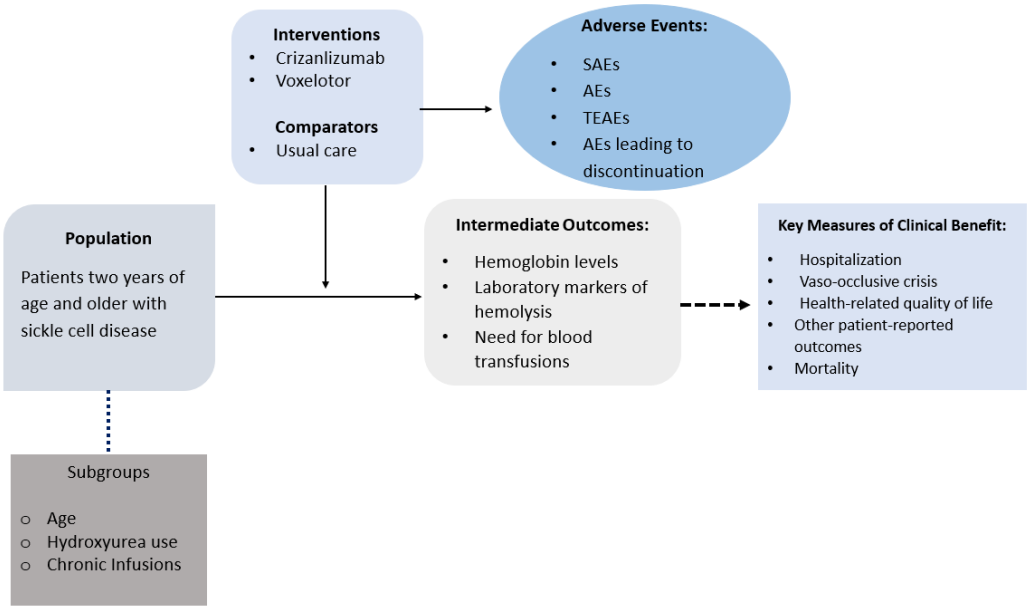
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will also be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The general analytic framework for assessment of therapies for sickle cell disease is depicted in Figure 1 on the following page.

Figure 1. Analytic Framework: Crizanlizumab and Voxelotor for Sickle Cell Disease



AE: adverse event, SAE: serious adverse event, TEAE: treatment emergent adverse events,

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., laboratory markers), and those within the squared-off boxes are key measures of benefit (e.g., vaso-occlusive crises). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. An arrow from interventions lead to the adverse events of treatment which are listed within the blue ellipse.

Populations

The population of focus for this review is children and adults two years of age and older diagnosed with SCD.

Interventions

The interventions of interest for this review are listed below:

- Crizanlizumab (investigational; Novartis) in addition to usual care (e.g., hydroxyurea, transfusions)
- Voxelotor (investigational; Global Blood Therapeutics) in addition to usual care (e.g., hydroxyurea, transfusions)

Comparators

We intend to compare each intervention to usual care alone. We do not expect to compare the interventions to each other.

Outcomes

The key outcomes of interest are described in Table 1 below.

Table 1. Key Outcomes and Harms

Outcomes	Key Harms
Mortality	Serious adverse events
Acute pain crisis (i.e., vaso-occlusive crisis)	Treatment-emergent adverse events
Hospitalization	Adverse events leading to discontinuation
Chronic pain	
Fatigue	
Cognitive effects	
Acute chest syndrome	
Mental health effects (e.g., depression, anxiety)	
Splenic sequestration	
Cardiovascular events (e.g., stroke and silent infarcts, pulmonary hypertension, heart failure)	
Hearing loss	
Vision loss	
Organ damage	
Pregnancy complications	
Quality of life	

Additional intermediate and surrogate outcomes of interest include:

- Hemoglobin levels
- Laboratory markers of hemolysis
- Need for blood transfusions

Timing

Evidence on intervention effectiveness and evidence on harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the US.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the interventions to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Table 2. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a Markov cohort model to assess the lifetime cost-effectiveness of the treatments of interest relative to relevant comparator treatments. The model structure will be based in part on a literature review of prior published models of sickle cell disease treatments and/or screening.[12-20] The base case analysis will take a health-system perspective (i.e., focus on direct medical care costs only). Data permitting, indirect costs will be considered in a separate analysis using a societal perspective. The target population will consist of children and adults ages two and older with sickle cell disease. The model will consist of health states including SCD with and SCD without VOC. Data permitting, we will also model health states for the sequelae of major morbidities of SCD, including stroke, myocardial infarction, pulmonary disease, chronic infection, and chronic pain, and disutilities associated with these acute vascular and infection events, as well as other events such as hospitalizations and acute chest syndrome. A cohort of patients will transition between states during annual cycles over a lifetime time horizon

(using a 3% discount rate for costs and outcomes), modeling patients from treatment initiation until death.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using clinical trial results for each treatment.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, AEs, and direct medical costs. The health outcome of each intervention will be evaluated in terms of VOCs avoided, life-years, equal value life years gained (evLYG), and quality-adjusted life years (QALYs) gained. Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity losses and other indirect costs will be included in a separate analysis, as data allow. Expected costs and outcomes will be tabulated for each treatment and its comparator, and results will be expressed in terms of the marginal cost per QALY gained, cost per life-year gained, cost per evLYG, and cost per VOC avoided.

In separate analyses, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2018/05/ICER-value-framework-v1-21-18.pdf.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by crizanlizumab or voxelotor (e.g., reductions in VOCs), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of sickle cell disease beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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