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Crizanlizumab, L-Glutamine, and Voxelotor for Sickle Cell Disease: Effectiveness and Value

Modeling Analysis Plan

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1. Approach

This analysis plan details our modeling approach and outcomes to be assessed for the economic evaluation of treatments for Sickle Cell Disease (SCD). Elements of this model analysis plan are subject to change as the project progresses. Refer to the research protocol for details on the systematic review of the clinical evidence on this topic.

The primary aim of this analysis will be to estimate the lifetime disability and costs of patients with sickle cell disease and to calculate the incremental cost-effectiveness of treatments for sickle cell disease using a Markov model. Crizanlizumab, L-glutamine and voxelotor will each be compared to usual care. The base-case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only), over a lifetime horizon and will include impacts on quality of life, including disability. Educational attainment, productivity impacts, and other indirect costs will be considered in a scenario analysis using a societal perspective, if data allow. The societal perspective for children will also consider school attendance and educational attainment. The model will be developed in Microsoft® Excel® 2013 (Version 17763).

2. Methods

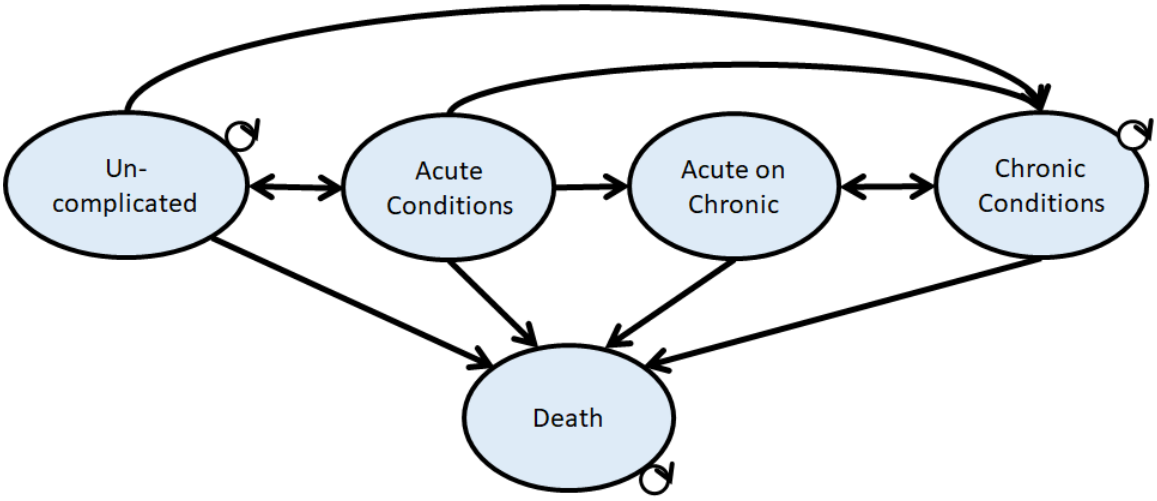
2.1 Overview and Model Structure

We will develop a *de novo* Markov model for this evaluation, informed by the best available evidence. The base-case analysis will take a health care sector perspective and thus focus on direct medical care costs only. Costs and outcomes will be discounted at 3% per year.

The model will focus on an intention-to-treat analysis, with a hypothetical cohort of patients with SCD being treated with usual care entering the model. Model cycle length will be one week to capture the short duration of some of the acute states. For acute states that generally last longer than one week, tunnel states will be used.

We will develop a Markov model for this evaluation, informed by key clinical trials, cohort studies, patient and clinical experts, and prior relevant studies of economic modeling in SCD. Figure 1 below illustrates the basic structure of the model.

Figure 1. Simplified Model Schematic



The model will focus on transitions between acute and chronic health states, as well as including risk of death. The acute and chronic conditions to be considered in the model are listed in Table 1. The inclusion of each condition in the model will be dependent on the available data and the evidence on the expected effect of treatments on each of the conditions. Treatments that delay or avoid acute and chronic conditions will improve patients' health and health care costs. Evidence for delay or avoidance of conditions may come directly from the trials. For treatments without direct evidence of the effect on these acute and chronic conditions, trial data that show a change in intermediate clinical outcomes (such as improved hemoglobin) will be used to estimate the effect on these conditions.

Table 1. Acute and Chronic Conditions Included in the Model

Clinical Outcomes	
Ischemia-Related Outcomes	
Acute	**Chronic**
Acute Pain Episode	Opioid Tolerance/Dependence
Acute Chest Syndrome	Pulmonary Hypertension
Myocardial Infarction	Heart Failure
Renal Infarction	Nephropathy, Chronic Kidney Disease
Stroke	Neurocognitive Impairment
Anemia-Related Outcomes	
Acute	**Chronic**
Acute Pain Episode	Opioid Tolerance/Dependence
Acute Chest Syndrome	Pulmonary Hypertension
Iron Overload Due to pRBCs	Heart Failure
Stroke	Nephropathy, Chronic Kidney Disease
	Neurocognitive Impairment
	Fatigue

pRBC: packed red blood cells

Treatments that affect ischemia or blood flow will have a direct effect in the model on acute pain episodes, acute chest syndrome, stroke, pulmonary hypertension, opioid tolerance/dependence, neurocognitive impairment and renal and myocardial infarction. Decreased myocardial and renal infarction will also lead to less heart and kidney failure. Treatments that affect anemia will have a direct effect in the model on acute pain episodes, acute chest syndrome and stroke. Reductions in anemia will also lead to a decreased need for chronic packed red blood cell transfusions and therefore less iron overload, and less kidney and heart failure. Serious adverse events for each treatment will also be included in the model.

The accumulation of chronic conditions will also be modeled; for example, a patient might have pulmonary hypertension, heart failure, and chronic kidney disease. Once a patient enters a chronic condition health state, it will be assumed that patients continue in that chronic health state. Patients that experience an acute clinical event on top of their existing chronic conditions will either continue in their same chronic health state, if the acute event resolves without sequelae, or will progress to a more complicated state if the acute event leads to an additional chronic disorder.

Since this model will reflect a lifetime of SCD, patients will remain in the model until they die. A patient can transition to death from any cause and from any health state.

2.2 Key Model Choices and Assumptions

Below is a list of key model choices:

Table 2. Model Assumptions

Assumption	Rationale
Health state costs based on current practice	Despite the heterogeneity in current treatment patterns, costs will be based on the best available data for both Medicaid and private insurance populations
Health state utility values will be used for chronic conditions and disutilities for acute conditions	This will allow decrements for acute conditions from a base of different chronic conditions
Changes in acute pain episodes are correlated with changes in the chronic conditions of interest	Changes in acute pain episodes reported in the trial will be linked to published data on the correlation of acute pain episodes and their effect on chronic conditions of interest
Changes in hemoglobin cause changes in the chronic conditions of interest	Changes in hemoglobin reported in the trials will be linked to published data on the correlation of hemoglobin and chronic conditions of interest. Clinical experts will be consulted where no published data exist.

2.3 Populations

The population of focus for the economic evaluation will be patients in the United States (US) diagnosed with SCD. In the base case, the model will test patient characteristics similar to those in the trials. The base-case model will use the lowest age from each trial for each respective treatment. Sensitivity analyses will extend trial results to younger populations, down to 5 years of age. Data permitting, we will include subgroup analyses based on sickle cell genotype, hydroxyurea use, and frequency of vaso-occlusive crises.

2.4 Interventions

The list of interventions of interest was developed with input from patient organizations, clinicians, manufactures, and payers. Choices of comparators were chosen to best reflect real-world treatment decisions and those in the clinical trials. The list of interventions and comparators is presented below:

- Crizanlizumab in addition to usual care
- Voxelotor in addition to usual care
- L-glutamine in addition to usual care

In the main analysis, each intervention will be compared to usual care, represented by the placebo arms of the relevant trials (which may include hydroxyurea and acute transfusions). However, based on patient input, a scenario analysis may be conducted where no treatment is considered standard of care and included as the comparator. Given that some of the treatments are weight-based, the dose of treatments will change over time as the modeled population ages and the average weight increases.

2.5 Input Parameters

Clinical Inputs

Transition Probabilities

For treatments that have demonstrated a direct impact on the outcomes of interest, this evidence will be used in the model to estimate the transitions between health states. For treatments that have not demonstrated a direct impact on the clinical outcomes of interest, we will attempt to model a best case scenario where a treatment's effect on intermediate outcomes, such as hemoglobin levels and hematocrit, along with evidence on their relationship to our outcomes of interest, will be used to estimate transitions between acute and chronic health states. Where evidence is lacking, we will solicit input from clinical experts and explore the impact of various assumptions through threshold analyses. Given the inherent uncertainty in using intermediate outcomes, assumptions will be described explicitly and robust sensitivity analyses will be undertaken.

Discontinuation

We will apply estimates of treatment discontinuation due to adverse events from the trial, along with assumptions for long-term discontinuation, as applicable for each comparator. Patients discontinuing their primary modeled treatment will be assumed to transition to usual care.

Mortality

In the base-case analysis, we will use probabilities derived from estimates of mortality for the SCD population from Hassell 2010[1] (Table 3), adjusted to include possible indirect improvements with treatment. The mortality estimates from Hassell are taken from compressed mortality reports by the CDC. The CDC collects and reports national mortality data from death certificates. In this case, ages were grouped in 5-year age brackets for deaths indicated as sickle cell anemia with or without crisis, double heterozygote sickling disorders, or other sickle cell disorders. In a scenario analysis, the model will only include direct and measured improvements in mortality from treatment.

Table 3. Annual Probabilities of Death by Age Group

Age Group	Percent of SCD Patients Who Died	Probability of Death	
		Per Age Group*	Annual
<1	1.5%	0.015	0.015
1-4	2%	0.0203	0.0051
5-9	1.5%	0.0155	0.0031
10-14	1.5%	0.0158	0.0032
15-19	4%	0.0428	0.0087
20-24	8%	0.0894	0.0186
25-34	20%	0.2454	0.0278
35-44	27%	0.4390	0.0562
45-54	20%	0.5797	0.0830
55-64	11%	0.7586	0.1325
65-74	2%	0.5714	0.0812
75-84	1.5%	1.0000	0.9688
85+	0%	-	-

SCD: sickle cell disease

*The probability of death per age group was calculated as the number of patients who died in that age group divided by the number of patients that were alive in that age group (i.e., 1 – proportion that had died previously).

Adverse Events

Adverse events (AEs) will be included based on those collected in each trial and from the published literature. AEs will not be included as their own health state; instead, costs of treating each AE will be added to the health state, weighted based on the probability of patients having an AE while on treatment. Similarly, utility decrements for AEs will be weighted by the probability of having each AE and subtracted from each health state while a patient is on treatment.

Health State Utilities

We will use consistent health-related quality of life (HRQoL; utility) values for each health state across the treatments evaluated in the model. A utility decrement will be applied to the cycle in which an acute event occurs. All utility values will be derived from publicly available literature and/or manufacturer-submitted data and applied to the modeled events.

To ensure the most recent utility values are used, we will undertake a systematic literature review using the terms in Table 4.

Table 4. Systematic Literature Search Terms

1	exp anemia, sickle cell/
2	((sickle adj3 (disease or an?emia)) or 'sickle cell' or meniscocyt* or drepanocyte* or sickl* or (SC adj3 (disease or an?emia))).ti,ab.
3	hemoglobin, sickle/ or (h?emoglobin adj5 sickl*).ti,ab.
4	((h?emoglobin or hb or hb- or hgb) adj3 (SS or S-S or SC or S-C or SB* or b0 or S-beta or thalassemia or beta-zero or beta plus)).ti,ab.
5	"Quality of Life"[Mesh]
6	"Cost-Benefit Analysis" [Mesh]

Searches will be run in EMBASE, Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE and Versions 1946 to Present. In a preliminary search we identified five sources providing HRQoL utility and disutility values for different health states of interest (Table 5).{Anie, 2012, 3012;(UK), 2012, 3011;McClish, 2005, 3010;Spackman, 2014, 3007;Cherry, 2012, 3004}

All possible values will be assessed based on the population, the utility measure, and the quality of the study. The base-case model will be based on the best available source.

Table 5: Preliminary HRQoL Values

Health State	Utilities	Source
SCD no pain	0.854-0.864	Spackman et al. 2013
SCD no pain	0.788	Anie et al. (raw data)
SCD no pain	0.717-0.700	McClish et al. 2005
SCD no pain	0.721	Anie et al. 2002
Sickle cell pain at admission to hospital	0.39	Anie et al. 2012
Sickle cell pain at discharge from hospital	0.65	Anie et al. 2012
Sickle cell pain at 1 week after admission to hospital	0.75	Anie et al. 2012

Drug Utilization

The following inputs will be used to model drug utilization and associated costs:

- Duration of treatment
- Schedule of doses for each drug in each regimen
- Protocol dosage for the indication (include information on vial sharing, dose wastage as applicable)

Table 6. Treatment Regimen Recommended Dosage

Generic Name	Crizanlizumab	Voxelotor	L-glutamine
Brand Name	Adakveo	n/a	Endari
Manufacturer	Novartis	Global Blood Therapeutics	Emmaus Life Sciences
Route of Administration	Intravenous	Oral	Powder, for oral solution
Dosing	5.0 mg/kg, administered at weeks 0, 2, and then every 4 weeks	1500 mg, once daily	5-15 grams, twice daily

n/a: not applicable

The following inputs may be used for scenario analyses of drug utilization and costs:

- Dose intensity adjustment factor
- Mean number of completed doses per patient

Cost Inputs

Drug Costs

We obtained the list prices for L-glutamine (Endari) and crizanlizumab (Adakveo). Because voxelotor is not approved by the FDA, its price is not yet available. However, analysts have estimated a price of approximately $100,000 per year[2], which we will use as a placeholder price until the price becomes available. We will also calculate the threshold prices at three thresholds: $50,000 per QALY gained, $100,000 per QALY gained, and $150,000 per QALY gained.

We will apply estimated branded drug discount rates to obtain net pricing estimates. Because crizanlizumab was recently approved, there are no data on net price available yet. Net price data for L-glutamine were not available in the SSR net price database.[3] We therefore used the FSS prices as the net prices for this drug.[4] Because crizanlizumab's net price is not yet known, we will use the average branded drug discount of 27% for branded drugs.[5] As part of standard care, we used the average of generic prices for hydroxyurea. If available, prices for the Medicaid payer will also be included.

Table 7. Drug Costs

Drug	WAC per Package/Vial[6]	Net Price Per Package/Vial	Discount From WAC	Net Price per Year§
L-glutamine (Endari®)*	$1,110 /package	$823.88†	26%	$10,031[a]-$30,092[b]
Crizanlizumab (Adakveo®)	$2,357/vial[7]	$1,720.61	27%	$35,355[c]-$176,775[d]
Voxelotor	NA	NA	NA	$100,000**
Hydroxyurea‡	$88.05/100 capsules	--	--	$322 - $2,251

NA: not available, WAC: wholesale acquisition cost
*Price per package of 60 5g packets
†Federal Supply Schedule (FSS) price as of November 2019
‡Average of generic prices for 100 500mg oral capsules
§1 year = 365.25 days or 52 weeks
**Analysts' estimated price
a price of 5mg BID, b price of 15mg BID
c price of 1 vial dose, d price of 5 vial dose

Please refer to the ICER Reference Case for more details on drug pricing.

Non-Drug Costs

We will explore obtaining estimates of other health care costs for sickle cell disease and related complications from claims and/or electronic health record data. If possible, costs will be stratified by payer type for use in payer-specific scenario analyses, such as Medicaid vs. commercial insurance. Costs that are not available from this analysis, including non-health care and other indirect costs, will be obtained from a search of the literature. Complication costs in the year of an event will reflect acute care and any subsequent care provided in the first year; history state costs will reflect annual resource use for the ongoing management of complications in subsequent years. Costs will be assessed from the perspective of a comprehensive US health care payer and will be inflated to 2019 dollars.

Literature suggests a hospitalization for painful crisis costs approximately $16,000 and acute chest syndrome costs $23,000. Other event costs are reported in Table 8.

Table 8. Non-Drug Costs

	Costs	Source
Painful Crisis	$15,556 per hospitalization	Bou-Maroun et al. 2017
Acute Chest Syndrome	$22,631 per hospitalization	Bou-Maroun et al. 2017
Stroke	$18,956 per hospitalization	Bou-Maroun et al. 2017
Splenic Sequestration	$14,858 per hospitalization	Bou-Maroun et al. 2017
Chelation Therapy	$18,762 per month	Master et al. 2016[8]
Transfusion	$199 per unit of blood	Gehrie et al. 2017[9]

2.6 Model Outcomes

Model outcomes will include equal value life years gained (evLYG), QALYs gained, pain crises avoided, increase in hemoglobin, and total costs for each intervention over a lifetime time horizon. Incremental analyses will report the cost per evLYG, cost per QALY, cost per pain crisis avoided and cost per 1 g/dL increase in hemoglobin. Costs and QALYs will also be reported by health state to understand the contribution of different cost elements to the total. All the costs and QALYs will be reported as discounted values, using a discount rate of 3% per annum. Undiscounted costs and QALYs will be presented for validation purposes.

2.7 Model Analysis

Cost-effectiveness will be estimated using the incremental cost-effectiveness ratios for each outcome (including cost per evLYG and cost per QALY) with incremental analyses comparing crizanlizumab, voxelotor and L-glutamine to usual care, from a health sector perspective in the base-case analyses. We will also consider methods to model the impact of treatments on health inequality/disparity by using a distributional cost-effectiveness framework and measures of inequality.[10]

Sensitivity Analyses

We will conduct one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses will also be performed by jointly varying all model parameters over the minimum numbers of simulations necessary to achieve statistical convergence, then calculating 95% credible range estimates for each model outcome based on the results. We will also perform threshold analyses for drug costs across a range of incremental cost-effectiveness ratios (from $50,000 to $150,000 per QALY).

Scenario Analyses

If data allow, we will consider conducting scenario analyses that include:

1) Modified societal perspective that includes components such as out-of-pocket costs, productivity losses, caregiver HRQoL, school attendance and educational attainment
2) Modeled time horizon
3) Sub-groups, as discussed previously

Model Validation

We will use several approaches to validate the model. First, we will provide preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using internal reviewers. External review will be undertaken by Sick Cells. As part of ICER's efforts in modeling transparency, we will also share the model with the relevant manufacturers for external verification around the time of publishing the draft report for this review. Finally, we will compare results to other cost-effectiveness models in this therapy area. The outputs from the model will be validated against the trial study data of the interventions and any relevant observational datasets.

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