Model-Projected Survival and Lifetime Clinical Outcomes of Exagamglogene Autotemcel (Exa-cel) in Patients With Sickle Cell Disease With Recurrent Vaso-Occlusive Crises in Canada

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BACKGROUND

- Sickle cell disease (SCD) is a rare blood disorder characterized by expression of abnormal sickle hemoglobin and vaso-occlusive crises (VOCs)[1-3]
- VOCs, caused by blockages of blood vessels, are a hallmark clinical manifestation of SCD and lead to development of acute and chronic organ complications[1-3]
- In Canada, the standard of care (SOC) for patients with SCD includes hydroxyurea and red blood cell transfusions[4]
- Exagamglogene autotemcel (exa-cel) is a cellular product consisting of autologous CD34$^+$ hematopoietic stem and progenitor cells (HSPCs) modified by non-viral, *ex vivo* CRISPR/Cas9 gene editing that reduces erythroid-specific expression of *BCL11A*, reactivating synthesis of fetal hemoglobin (HbF). Increases in HbF levels ameliorate the severity of SCD and thus has the potential to eliminate VOCs and provide a functional cure for patients with SCD with recurrent VOCs[5]
  - In the Phase 3 pivotal trial CLIMB SCD-121 (June 2023 data cut), 97% (29/30) of participants with sufficient follow-up treated with exa-cel met the primary endpoint of VF12 (freedom from severe VOCs for at least 12 consecutive months); among these 29 participants, the mean duration of freedom from VOCs was 22.4 months (range, 14.8 to 45.5)
- Based on the positive results from the CLIMB SCD-121, Health Canada granted marketing authorization for exa-cel for the treatment of patients aged ≥12 years with SCD with recurrent VOCs in September 2024

OBJECTIVE

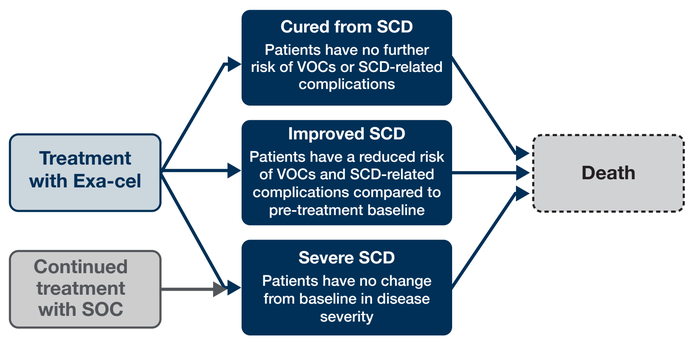
- To assess the potential survival and lifetime clinical outcomes of exa-cel versus SOC in Canada for patients with SCD with recurrent VOCs

METHODS

Model Overview

- A Markov cohort model was developed to project survival and clinical outcomes of patients with SCD with recurrent VOCs treated with exa-cel versus SOC in Canada over a lifetime horizon
- The Markov model includes health states defined by the occurrence of VOCs which are assumed to impact the risk of developing SCD-related complications as well as a health state for death (**Figure 1**)
  - The "cured" health state, for patients with successful engraftment of exa-cel who achieved VF12, defined in the Phase 3 pivotal trial CLIMB SCD-121 as not experiencing any protocol-defined severe VOCs for at least 12 consecutive months in the 24 months following exa-cel infusion
  - The "improved" health state, for patients that did not achieve VF12 but had a reduction in the rate of VOCs compared to pre-treatment baseline
  - The "severe SCD" health state, for patients that did not experience any change in VOCs from pre-treatment baseline
- All patients enter the model in the severe SCD health state
- Patients receiving SOC are assumed to remain in the severe SCD health state and maintain the same frequency of VOCs from baseline until the end of the model horizon
- Patients treated with exa-cel can potentially transition into the "cured" or "improved disease" health states; patients are assumed to remain in the same health state for the entire model time horizon
  - Patients treated with exa-cel were assumed to continue to experience VOCs at the baseline frequency during the one-year period over which the transplant occurred
- Mortality risk is estimated based on the health state, frequency of VOCs, and occurrence of complications and other transplantation-related events

Figure 1. SCD Markov Model Structure



SCD: sickle cell disease; **SOC:** standard of care

Data Sources and Model Inputs

- A cohort of patients with SCD with recurrent VOCs was modeled from baseline – the cohort had a mean age of 22.1 years and was assumed to experience 3.9 VOCs per year at baseline, based on the baseline characteristics of participants enrolled in the Phase 3 pivotal trial CLIMB SCD-121[5]
- Exa-cel clinical efficacy was informed by the interim analysis of the CLIMB SCD-121 trial published in Frangoul et al. 2024 *N Engl J Med*[5] (data as of June 2023; median follow-up: 19.3 months; range: 0.8 months to 48.1 months):
  - 97% of patients treated with exa-cel were assumed to achieve the "cured" health state. This assumption was based on 29 of 30 participants with sufficient follow-up treated with exa-cel that met the primary endpoint of VF12
  - The remaining 3% of patients treated with exa-cel remained in the severe SCD health state, given 1 trial patient with a medical history of chronic pain from SCD did not meet the primary endpoint
- Model inputs for baseline prevalence of chronic SCD-related complications were based on CLIMB SCD-121; monthly risks/rates for experiencing SCD-related complications were derived from a published retrospective database analysis of patients with SCD with recurrent VOCs in Ontario, Canada[6] (**Table 1**)
  - Patients treated with exa-cel who achieve the "cured" health state were assumed to be at no further risk of developing SCD-related complications
- Age-specific annual mortality risks for SCD in the absence of complications were based on published literature[7], as were the inputs that informed the increased risk of mortality associated with VOCs and SCD-related complications (**Table 2**)
  - Mortality for patients cured from SCD was assumed to be 25% higher than the age- and gender-specific mortality rates in the Canadian general population to account for the potential impact of previous SCD and use of myeloablative conditioning as part of the exa-cel treatment process

Table 1. Rates and Risk of Developing SCD-Related Complications

Complication	Severe SCD	Improved Disease	Source
Acute complications (monthly rate)			
Acute chest syndrome	0.0034	0.0016	Lilly et al. 2024[6]
Stroke*	0.0009	0.0006	Lilly et al. 2024[6]
Acute infections	0.0059	0.0017	Lilly et al. 2024[6]
Acute renal failure	0.0073	0.0016	Lilly et al. 2024[6]
Gallstones	0.0073	0.0024	Lilly et al. 2024[6]
Pulmonary embolism	0.0057	0.0011	Lilly et al. 2024[6]
Leg ulcers	0.0015	0.0006	Lilly et al. 2024[6]
Chronic complications (monthly risk)			
Pulmonary hypertension	0.079%	0.022%	Lilly et al. 2024[6]
Chronic kidney disease	0.057%	0.042%	Lilly et al. 2024[6]
Avascular necrosis	0.385%	0.133%	Lilly et al. 2024[6]
Neurocognitive impairment	0.031%	0.007%	Lilly et al. 2024[6]
Retinopathy	0.101%	0.052%	Lilly et al. 2024[6]
Heart failure	0.088%	0.030%	Lilly et al. 2024[6]
Liver complications	0.072%	0.027%	Lilly et al. 2024[6]

* 35% of patients with stroke were assumed to incur long-term costs/disutility

Table 2. Mortality Associated with SCD-Related Complications

Complication	Hazard Rate	Source
Acute complications		
VOC	1.56	Shah et al. 2019[8]
Acute chest syndrome	1.27	Elmariah et al. 2014[9]
Acute renal failure	9.50	Yeruva et al. 2016[10]
Pulmonary embolism	2.75	Brunson et al. 2017[11]
Leg ulcers	1.66	Elmariah et al. 2014[9]
Stroke	7.7%*	Bradt et al. 2020[7]
Chronic complications		
Chronic kidney disease	9.57	Bradt et al. 2020[7]
Pulmonary hypertension	12.57	Bradt et al. 2020[7]
Heart failure	12.57	Bradt et al. 2020[7]
Liver complications	2.53	Gardner et al. 2016[12]

*Applied as an instant risk of death.

Model Outcomes

- The following outcomes were projected by the model:
  - Mean life expectancy
  - Mean number of VOCs over patient lifetime
  - Number of acute complication events over patient lifetime
  - Proportion of patients developing chronic complications
- All outcomes are undiscounted

Scenario Analyses

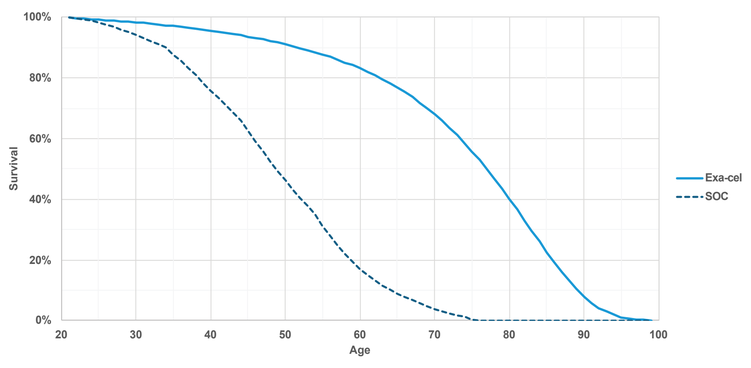
- Model parameters were varied to examine the impact of alternative inputs on clinical outcomes, including:
  - *Population:* A cohort with mean age of 12 years with no baseline chronic complications
  - *Disease severity*: A cohort of patients with 5.6 VOCs/year based on a claims database study in Ontario, Canada of patients with SCD with ≥ 2 VOCs per year during the follow up period
  - *Disease severity:* A more severe cohort experiencing 18.5 VOCs/year at baseline, the highest number of baseline VOCs among participants enrolled in the CLIMB SCD-121 trial
  - *Mortality:* Risk of mortality based on standardized mortality ratios (SMRs) derived from a published retrospective cohort study of patients with SCD with recurrent VOCs in Ontario Canada (SMR: Improved: 5.20; Severe SCD: 30.80)[6]

RESULTS

Base Case Results

- Over a lifetime horizon, patients treated with exa-cel had a substantial increase in survival of 24.6 years compared to patients treated with SOC (**Table 3**)
  - The mean predicted survival (i.e., age at death) of patients receiving exa-cel was 74.3 years vs. 49.7 years for patients treated with SOC (**Table 3**)
- Patients treated with exa-cel experienced a substantial reduction in the number of VOCs over the lifetime horizon compared to SOC (exa-cel: 7.4 vs. SOC: 107.8) (**Table 3**)
- The lifetime burden of all acute and chronic complications of SCD was projected to be substantially lower in patients treated with exa-cel than in those receiving SOC (**Table 3**)

Figure 2. Projected Survival for Patients with SCD



SOC: standard of care

Author Disclosures

LK, SK, and **AZ** are employees of Eversana. **CU, MG, SJ,** and **AL** are employees of Vertex Pharmaceuticals Incorporated and may hold stock or stock options in the company.

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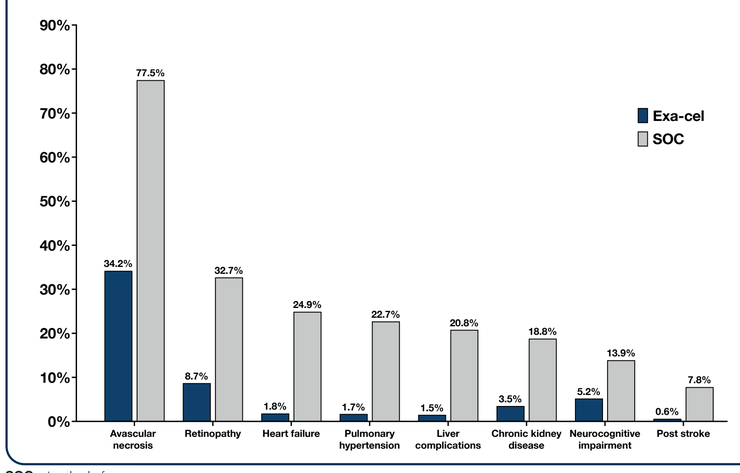
Table 3. Projected Clinical Outcomes Over a Lifetime Horizon

Outcome	Exa-cel	SOC	Δ, Exa-cel vs SOC
Survival			
Mean life years (from model start)	52.2	27.6	24.6
Mean age of death (years)	74.3	49.7	24.6
Mean number of VOCs over a lifetime			
VOCs	7.4	107.8	-100.4
Mean number of acute complication events over lifetime per person			
Acute chest syndrome	0.076	1.114	-1.038
Stroke	0.021	0.308	-0.287
Acute infection	0.135	1.973	-1.838
Acute kidney injury/failure	0.164	2.405	-2.241
Gallstones	0.166	2.428	-2.263
Pulmonary embolism	0.129	1.890	-1.761
Leg ulcers	0.034	0.501	-0.466

SOC: standard of care

Figure 3. Proportion of Patients With Chronic Complications Over a Lifetime Horizon



SOC: standard of care

Scenario Analyses Results

- Patients treated with exa-cel had an increase in survival ranging from 24.6 years to 34.1 years compared to SOC, across the various scenarios analyzed (**Table 4**)

Table 4. Scenario Analysis Results

Outcome	Incremental mean LYs (Exa-cel vs SOC)	Incremental mean number of VOCs (Exa-cel vs SOC)
Base case	24.6	-100.4
Population: Age 12 years	29.8	-122.5
Severity: 5.6 VOCs/year	24.7	-144.5
Severity: 18.5 VOCs/year	25.5	-457.5
Mortality: SMR-based mortality inputs	34.1	-75.5

*Applied as an instant risk of death.
LY: life years; **SMR:** standardized mortality ratio; **SOC:** standard of care; **VOC:** vaso-occlusive crises

Limitations

- Health care decision analytic models based on VOCs and complications could oversimplify the complexity of SCD pathophysiology given the impact of hemolysis and changes to vasculature on SCD-related acute and chronic complications
- As a simplifying assumption, patients treated with SOC were assumed to experience a static 3.9 VOCs per year over the lifetime horizon; rate of VOCs was not assumed to be dependent on age or other clinical characteristics
- Life-time clinical efficacy inputs for exa-cel were based on up to 48.1 months of clinical data[5]; however, given the mechanism of action for exa-cel, treatment durability is expected to be life-long

CONCLUSIONS

- **Model projections suggest that exa-cel could substantially improve survival and lower the incidence of VOCs and complications in patients with SCD with recurrent VOCs in Canada compared to treatment with SOC**

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