EE173

Economic Evaluation of Exagamglogene Autotemcel (Exa-cel) Gene-Edited Therapy in Patients With Sickle Cell Disease With Recurrent Vaso-Occlusive Crises

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INTRODUCTION

- Sickle cell disease (SCD), a rare hereditary blood disorder, is characterized by expression of abnormal sickle hemoglobin[1-3]
  - Vaso-occlusive crises (VOCs), caused by blockages of blood vessels, are a hallmark clinical manifestation of SCD and lead to development of acute and chronic organ complications[2,3]
- The current standard of care (SOC) for patients with SCD includes hydroxyurea and red blood cell transfusions
- Exagamglogene autotemcel (exa-cel), formerly known as CTX001, is a cellular product consisting of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) modified by nonviral, *ex vivo* CRISPR/Cas9 that reduces erythroid-specific expression of *BCL11A*, which leads to an increase in fetal hemoglobin (HbF) levels and thus has the potential to eliminate VOCs in patients with SCD with recurrent VOCs[4]
- Exa-cel is a one-time potentially curative therapy being evaluated for patients with SCD with recurrent VOCs
  - In the pivotal clinical trial of exa-cel in SCD, recurrent VOCs were defined based on the experience of ⩾2 VOCs/year for 2 consecutive years[4]
- Data on exa-cel to date have shown an elimination of VOCs in all 31 patients treated with exa-cel (duration from 2.0 months to 32.3 months)[4]

OBJECTIVE

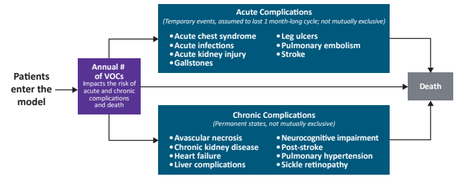
- To assess the potential cost-effectiveness of exa-cel versus SOC in the United States (US) for patients with SCD with recurrent VOCs

METHODS

Model Overview

- A Markov cohort model was developed to compare the expected cost and health outcomes of patients treated with exa-cel versus SOC over a lifetime horizon from a US payer and societal perspective
- In the model, the risk of developing acute or chronic complications is estimated based on the frequency of VOCs (**Figure 1**)

Figure 1. Schematic of SCD Model Structure



SCD, sickle cell disease; VOC, vaso-occlusive crisis.

- All patients treated with exa-cel are assumed to achieve a curative state based on the published results of the pivotal clinical trial CLIMB SCD-121[4]
  - Patients cured of SCD are assumed to have no further risk of VOCs or SCD-related complications
  - Patients treated with exa-cel are assumed to remain cured for the remainder of the lifetime horizon (i.e., not experience treatment waning)
- Patients receiving SOC are assumed to maintain the same frequency of VOCs from baseline until the end of the model horizon
- Mortality risk is estimated based on whether patients are cured, the incidence/prevalence of acute/chronic complications, and the occurrence of other transplantation-related events

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 22.5 years and was assumed to experience 3.9 VOCs per year at baseline based on the characteristics of patients enrolled in the CLIMB SCD-121 trial of exa-cel[4]
  - Patients were assumed to have no SCD-related chronic complications at baseline
- Exa-cel clinical efficacy was informed by the results of the CLIMB SCD-121 trial (up to 32.3 months of follow-up)[4]
- The risk of developing SCD-related acute and chronic complications, as a function of rate of VOCs, was derived from published literature[5-9]; the model combines the incidence of complications expected in the absence of VOCs with a hazard ratio to capture the increased risk of developing complications with more frequent VOCs[5-9] (model input values presented previously[10])
- Age-specific annual mortality risks for SCD in the absence of complications were based on published literature, as were the inputs that informed the increased risk of mortality associated with VOCs and SCD-related complications[5-7,11-13] (model input values presented previously[10])
  - Mortality for patients cured of SCD was assumed to be 25% higher than the age- and gender-specific mortality rates in the general US population to account for the potential impact of previous SCD and use of myeloablative conditioning
- Disease-related cost inputs were derived from published literature and US-specific databases (e.g., REDBOOK for drug costs) (**Table 1**)
  - Disease-related costs included the cost of treating VOCs, managing acute and chronic SCD-related complications, disease monitoring (routine lab tests and physician visits), treating serious adverse events associated with SOC, and potential fertility treatments for patients treated with exa-cel
- Utility inputs for SCD in the absence of complications and for patients cured of SCD, as well as inputs for managing VOCs and acute and chronic SCD-related complications, were derived from published literature (**Table 1**)
- The societal perspective included costs associated with patient and caregiver work productivity and patient out-of-pocket costs, as well as caregiver disutility associated with SCD-related complications and patient death
  - Patient employment, absenteeism, and presenteeism rates were dependent on the frequency of VOCs and informed by available literature[7,14,15]; patients cured of SCD were assumed to return to work and have no further disease-related absenteeism/presenteeism

Table 1. Key Disease-Related Cost and Utility Model Inputs

	Disease-Related Cost		Utility	
	Input Value[a]	Source	Input Value	Source
Uncomplicated SCD	–	–	0.80	Bradt, et al[7]; Anie, et al[23]
Cured of SCD	–	–	0.95	O'Brien, et al[24]
Acute complications	**Cost per event, $**		**Disutility**	
VOC	14,531	Bradt, et al[7]	–0.18	NICE[5]
Acute chest syndrome	31,628	Bradt, et al[7]	–0.56	NICE[5]
Stroke	61,127	Bradt, et al[7]	–0.57	Jiao, et al[26]
Acute kidney injury	8,680	Bradt, et al[7]	–0.14	Bradt, et al[7]
Pulmonary embolism	10,673	Fanikos, et al[16]	–0.05	Ojelabi, et al[25]
Acute infections	28,720	Zimlichman, et al[17]	–0.16	NICE[5]
Gallstones	1,366	CMS[18]	–0.12	NICE[5]
Leg ulcers	9,086	Rice, et al[19]	–0.11	NICE[5]
Chronic complications	**Annual cost, $**		**Disutility**	
Pulmonary hypertension	20,464	Bradt, et al[7]	–0.21	NICE[5]
Chronic kidney disease	21,908	Bradt, et al[7]	–0.14	Bradt, et al[7]
Avascular necrosis	53,284	Hansen, et al[20]	–0.05	Ojelabi, et al[27]
Post-stroke	10,375	Bradt, et al[7]	–0.13	Cherry, et al[28]
Neurocognitive impairment	12,364	Bradt, et al[7]	–0.05	Stites, et al[29]
Retinopathy	4,325	Wittenborn, et al[21]	–0.05	Ojelabi, et al[27]
Heart failure	34,388	Bradt, et al[7]	–0.12	Bradt, et al[7]
Liver complications	15,594	Stepanova, et al[22]	–0.05	Ojelabi, et al[27]

CMS, Centers for Medicare & Medicaid Services; NICE, National Institute for Health and Care Excellence; SCD, sickle cell disease; VOC, vaso-occlusive crisis.
[a]All costs were inflated to 2022 USD using the Consumer Price Index.

Model Outcomes

- The following outcomes were modeled:
  - Mean life years (LYs) and quality-adjusted life years (QALYs)
  - Number of VOCs and acute complication events
  - Proportion of patients developing chronic complications
  - Mean disease-related costs and indirect costs
  - Cost-effective price of exa-cel at a willingness-to-pay (WTP) threshold of $150,000 per QALY gained
- Outcomes were discounted at an annual rate of 3.0%

Scenario and Sensitivity Analyses

- A deterministic sensitivity analysis was performed to assess the robustness of model parameters, including baseline cohort characteristics, rates of SCD-related complications, mortality, cost, and utility inputs
- Scenario analyses were conducted to examine the impact of alternative inputs on model outcomes, including:
  - A cohort with mean age of 12 years who experienced 2 VOCs/year at baseline, based on the minimum requirements for CLIMB SCD-121 trial eligibility
  - A more severe cohort experiencing 10 VOCs/year at baseline, consistent with previous economic modeling conducted for SCD[7]
  - Utilizing the general population complication risks for patients cured of SCD (as opposed to no risk in base case)

RESULTS

Base Case Results

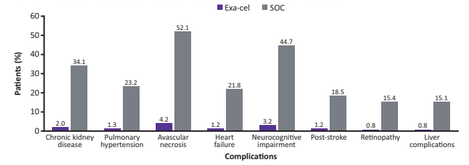
- Over a lifetime horizon, patients treated with exa-cel had a substantial increase in survival of 23.3 years compared to SOC (**Table 2**)
  - The mean predicted survival (i.e., age at death) of patients receiving exa-cel was 67.8 years versus 44.5 years for patients treated with SOC
- Patients treated with exa-cel experienced a substantial reduction in the number of VOCs over the lifetime horizon compared to SOC (exa-cel: 4 vs SOC: 86)
  - Patients treated with exa-cel were assumed to continue to experience VOCs at the baseline frequency during the 1-year period over which the transplant occurred
- Exa-cel was associated with substantial improvements in health-related quality of life, as demonstrated by the gain of 26.1 additional undiscounted QALYs (11.9 discounted QALYs) compared to SOC
- When incorporating caregiver disutility, the incremental QALYs gained provided by exa-cel compared to SOC increased (27.3 undiscounted QALYs, 12.4 discounted QALYs)
- The lifetime burden of acute and chronic complications due to SCD was projected to be lower in patients treated with exa-cel than in those receiving SOC (**Table 2**; **Figure 2**)

Table 2. Projected Clinical Outcomes

	Exa-cel	SOC	Δ, Exa-cel vs SOC
LYs			
Undiscounted	45.3	22.0	**+23.3**
QALYs			
Undiscounted (payer perspective)	37.2	11.0	**+26.1**
Undiscounted (societal perspective[a])	35.5	8.2	**+27.3**
Number of VOCs over a lifetime	4	86	**–82**
Mean number of SCD-related acute complication events over a lifetime			
Acute chest syndrome	0.06	1.32	**–1.26**
Stroke	0.04	0.77	**–0.74**
Acute infection	0.33	7.34	**–7.00**
Acute kidney injury/failure	0.02	0.43	**–0.41**
Gallstones	0.05	1.01	**–0.96**
Pulmonary embolism	0.02	0.47	**–0.44**
Leg ulcers	0.14	3.09	**–2.95**

exa-cel, exagamglogene autotemcel; LY, life year; QALY, quality-adjusted life year; SOC, standard of care; VOC, vaso-occlusive crisis.
[a]Includes caregiver disutilities.

Figure 2. Proportion of Patients Developing SCD-Related Chronic Complication

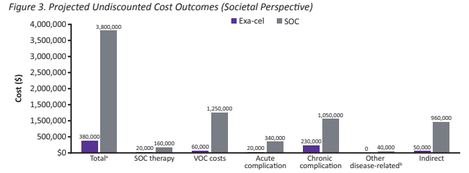


exa-cel, exagamglogene autotemcel; SOC, standard of care.

Base Case Results

- In addition to providing more than 20 additional years of survival, exa-cel was projected to provide undiscounted cost savings of ~$2,510,000 per patient in SCD management costs over the lifetime horizon, 93% ($2,330,000) of which was attributable to the reduction in costs of SCD complication management (including VOCs) (**Figure 3**)
- Treatment with exa-cel was associated with an additional $900,000 in undiscounted cost savings from the societal perspective, the majority of which were attributed to reduced costs associated with patient absenteeism/presenteeism

Figure 3. Projected Undiscounted Cost Outcomes (Societal Perspective)



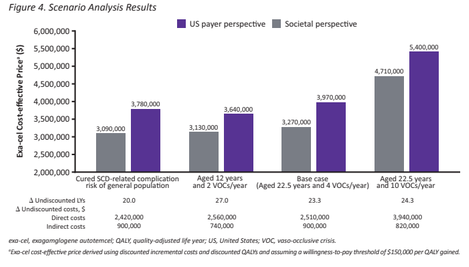
exa-cel, exagamglogene autotemcel; SOC, standard of care; VOC, vaso-occlusive crisis.
[a]Total disease related costs and indirect costs (does not include exa-cel treatment-related costs); [b]Other costs include routine disease monitoring costs, adverse event costs, and fertility costs. Other costs for exa-cel were rounded down from ~$4,000.

- Over a lifetime, exa-cel was estimated to provide 11.9 discounted QALYs and $1,710,000 in discounted savings in disease-related costs from the US payer perspective; at a WTP threshold of $150,000/QALYs gained, exa-cel is expected to be cost-effective at a price of ~$3,270,000 (**Figure 4**)
- From the societal perspective, the cost-effective price of exa-cel increases to $3,970,000

Scenario and Sensitivity Analyses

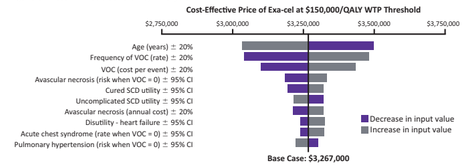
- The cost-effective price of exa-cel ranged from $3,090,000 to $5,400,000 across the various scenarios conducted from both the US payer and societal perspectives (**Figure 4**)
- The cost-effective price of exa-cel was most sensitive to the baseline frequency of VOCs, baseline age, VOC cost, complication risks, and utility values for cured/uncomplicated SCD (**Figure 5**)

Figure 4. Scenario Analysis Results



exa-cel, exagamglogene autotemcel; QALY, quality-adjusted life year; US, United States; VOC, vaso-occlusive crisis.
[a]Exa-cel cost-effective price derived using discounted incremental costs and discounted QALYs and assuming a willingness-to-pay threshold of $150,000 per QALY gained.

Figure 5. Deterministic Sensitivity Analysis



CI, confidence interval; exa-cel, exagamglogene autotemcel; QALY, quality-adjusted life year; SCD, sickle cell disease; VOC, vaso-occlusive crisis; WTP, willingness-to-pay.

LIMITATIONS

- Healthcare decision analytic models based on VOCs alone could oversimplify the complexity of SCD pathophysiology given the impact of hemolysis and changes to vasculature on SCD acute and chronic complications
- As a simplifying assumption, the modeled cohort was assumed to experience 3.9 VOCs per year over the lifetime horizon; rate of VOCs was not assumed to depend on age or other clinical factors
- The model did not estimate the impact of newer SCD therapies (i.e., crizanlizumab, voxelotor, and L-glutamine) on clinical outcomes; previous literature suggests including these therapies may lead to modest improvement in clinical outcomes in patients with SCD at significant increased cost[7] and would likely result in a higher cost-effective price for exa-cel if included
- Lifetime clinical efficacy inputs for exa-cel were based on up to 32.3 months of clinical data; however, given the mechanism of action for exa-cel, treatment durability is expected to be lifelong
- Exa-cel is an investigational therapy that has not been approved by any regulatory authority at this time

CONCLUSIONS

- Model projections suggest that exa-cel could substantially improve survival and quality of life, reduce the incidence of VOCs and SCD-related complications, and provide substantial cost savings from reduced disease burden in patients with SCD with recurrent VOCs compared to treatment with current SOC
- Utilization of the societal perspective incorporates a more holistic evaluation of impact of a potentially curative therapy
- Cost-effective prices for exa-cel ranged from ~$3.1M to $5.4M; utilization of the societal perspective led to higher cost-effective prices

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AUTHOR DISCLOSURES

CU, NL, SJ, and AL are employees of Vertex Pharmaceuticals Incorporated and may hold stock or stock options in the company. YX, HY, and XC are employees of Analysis Group, Inc. and received consulting fees from Vertex to conduct the study. FJO has nothing to disclose. UM is a former employee of Vertex Pharmaceuticals Incorporated and may hold stock or stock options in the company. JW is a former employee of Analysis Group, Inc. and received consulting fees from Vertex to conduct the study.

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