An Innovative Approach to Incorporating Health Inequalities Into HTA Decision Making as Demonstrated by Exagamglogene Autotemcel (Exa-cel) in Patients With Sickle Cell Disease in the United Kingdom and Canada

Gabriela Vega-Hernandez[1]; Michael Gargano[1]; Andrea Lopez[1]; Chuka Udeze[1]; Joshua Soboil[2]

1. Vertex Pharmaceuticals, Boston, MA United States; 2. Cogentia Healthcare Consulting, Cambridge, United Kingdom

Poster EE386

BACKGROUND

- Sickle cell disease (SCD) is a rare blood disorder characterized by the expression of abnormal sickle hemoglobin and vaso-occlusive crises (VOCs), which can lead to the development of acute and chronic organ complications and contributes to patients having a lifespan several decades shorter than that of the general population. Patients with severe SCD, defined as 2 or more annual VOCs, typically see an even further reduction in life expectancy[1-3]
- SCD predominantly affects individuals of African or Caribbean heritage, who disproportionately experience health inequalities; it has been reported that these patients experience sub-optimal care, with low disease awareness from healthcare professionals, and a history of inadequate healthcare investment potentially leading to inequalities[4,5]
- Current value assessment frameworks applied in health technology assessments (HTAs) fail to properly capture the benefits that highly innovative therapies can bring to underserved populations in regards to health inequality. There is currently no mechanism for a fairer displacement of resources to treat these populations and alleviate the disparities compared to the general population
- On the other hand, available methodologies to estimate the impact of a new intervention on health inequalities are very complex and require a wealth of data, which is often scarce in underserved populations to begin with, making it unfeasible to carry out such type of analyses
- The current analysis proposes an innovative approach to incorporating the impact of health inequalities into HTA decision making through the use of a distributional cost-effectiveness analysis (DCEA) applied in the HTA assessment of exagamglogene autotemcel (exa-cel) in the UK and Canada
- 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 has the potential to provide a functional cure for patients with SCD with recurrent VOCs[6]
- In clinical trials, exa-cel has demonstrated clinical benefit in terms of elimination of VOCs and hospitalizations, and additional quality of life benefits[6]. It has been approved for marketing authorization in multiple countries, including the UK where it received a positive HTA recommendation from the National Institute for Health and Care Excellence (NICE) in January 2025, and Canada where it received a positive HTA recommendation from Canada's Drug Agency (CDA) in January 2025[7-9]

OBJECTIVE

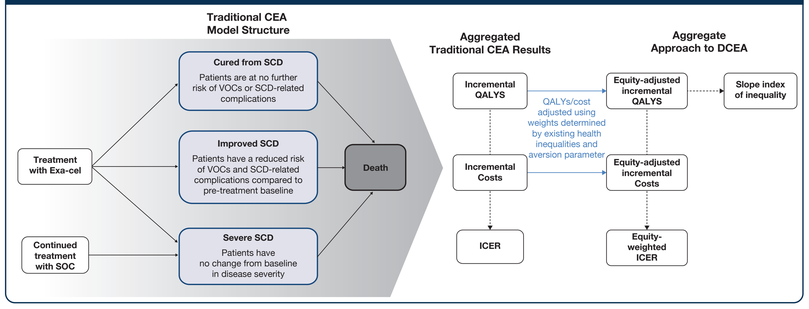
To present a novel approach using a DCEA to address the impact of highly innovative therapies on health inequalities during the HTA decision making process using the recent example of exa-cel for the treatment of patients with SCD with recurrent VOCs in the UK and Canada.

METHODS

Model Overview

- An aggregate approach was taken wherein a DCEA component was built on top of existing Markov cost-effectiveness models in the UK and Canada[10,11] comparing treatment with exa-cel versus standard of care (SOC), namely hydroxyurea, red blood cell transfusions, and/or iron chelation therapy (**Figure 1**)
- In addition to traditional CEA outcomes (i.e., costs, quality adjusted life years [QALYs], incremental cost-effectiveness ratios [ICERs]), the model output included health equity outcomes such as the change in slope index of inequality (SII), the equity-weighted ICER, and the equity-adjusted net health benefit
- Health inequality was measured using the index of multiple deprivations (IMD), an instrument which takes into account factors such as income, employment, education, health, crime, barriers to housing and services, and living environment[12]
  - Patients were divided into IMD quintiles - where IMD 1 represents patients facing the greatest inequality and IMD 5 represents patients facing the least inequality
  - IMD was used as a proxy for deprivation experienced by ethnic groups more likely to have SCD, but is not itself directly connected with patient race or ethnicity

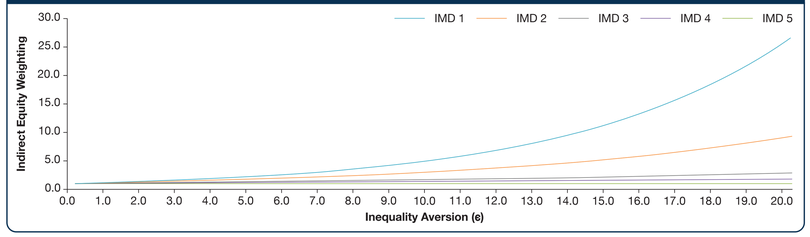
Figure 1. DCEA Based on SCD Markov Model Structure



CEA, cost-effectiveness model; **DCEA**, distributional cost-effectiveness model; **exa-cel**, exagamglogene autotemcel; **ICER**, incremental cost-effectiveness ratio; **SCD**, sickle cell disease; **SOC**, standard of care; **QALY**, quality adjusted life years; **VOC**, vaso-occlusive crisis.

- The SII measures the difference in quality adjusted life expectancy (QALEs) between the least and most deprived portions of a population. The SII was estimated as the slope of an Ordinary Least Squares regression equation which regressed QALEs at birth on the fractional rank of the equity (IMD) groups[13]
- For the estimate of post-intervention SII, the regressed QALEs were adjusted to reflect the benefit provided by exa-cel. Specifically, the discounted incremental QALYs gained from the use of exa-cel versus SOC (from the traditional CEA) were proportionally allocated to the IMD quintiles based on the distribution of patients in the eligible treated population. For each IMD group, the incremental QALYs were then added to the corresponding pre-intervention QALEs
- The population-level change in health inequality was then estimated by multiplying the change in SII (i.e., the difference in the fitted regression pre- and post-intervention) by the total general country population
  - A negative change in SII indicates that the health intervention reduces population-level health inequality
  - Per expert opinion, a change of more than 10-12k in SII is considered substantial relative to most healthcare expenditure decisions
- The model also calculated a novel health equity outcome, the equity-weighted ICER, wherein outcomes are adjusted to take into account a decision-maker's aversion to inequality and their willingness to reduce health inequality at the possible expense of greater increases in total population health. This sentiment is measured using the Atkinson inequality aversion parameter (ε)[14]
- The derivative of the Atkinson social welfare function was used to calculate indirect equity weights for each IMD quintile (**Figure 2**)
  - Weights are a function of the Atkinson inequality aversion parameter and the QALE of each quintile
  - Each weight is relative to the IMD 5 population to ensure that the least deprived population does not have a weight less than 1, which would lead to a QALY being valued less than its non-equity weighted counterpart
- Model outcomes (namely gross health benefit and health opportunity cost) were divided into IMD groups and the IMD-specific equity weights for the chosen Atkinson inequality aversion parameter were applied
  - Once these were calculated, the ratios of health opportunity costs to traditional costs and equity-weighted QALYs (derived from gross health benefit) to traditional QALYs were calculated and applied as weights to the traditional model's outcomes to calculate the final equity-weighted ICER

Figure 2. Indirect Equity Weights by IMD Quintile



IMD, index of multiple deprivations.

Model Overview, Continued

- The model also calculated the net health benefit in each IMD quintile to show how patients in different quintiles would be affected by the adoption of exa-cel
- ICERs were discounted at 1.5%
- DCEA methodology and novel outcomes were presented and accepted by HTAs as part of the submissions for exa-cel to NICE in the UK and CDA in Canada[8,9]

Data Sources and Model Inputs

- Inputs for the underlying UK and Canada exa-cel CEAs have been previously presented[10-11]; DCEA inputs are presented in **Table 1**
- An Atkinson inequality aversion parameter of 11.0 was applied for the UK analysis; this value was sourced from a study which performed an online survey of the general English population in order to specifically elicit aversion parameters[14]
  - The same value was applied in the Canadian analysis, given the lack of a Canadian-specific aversion parameter study or value
- The QALEs and proportion of the general population in each IMD quintile in the UK and Canada were sourced from published literature[16-18]

Table 1. DCEA Model Inputs

Input	UK	Canada	Source
Total eligible treatment population size	1,790	1,069	UK: Vertex Data on file[15] CA: Vertex Data on file[15]
Total general population size	56,536,419	40,769,890	UK: ONS 2022[19] CA: Statistics Canada 2024[20]
Atkinson Inequality Aversion Parameter (ε)	11.0		Robson et al., 2017[14]
Quality-adjusted life expectancy			
IMD 1 (most deprived)	62.2		Love-Koh et al., 2023[16]
IMD 2	65.5		
IMD 3	69.5		
IMD 4	71.1		
IMD 5 (least deprived)	73.3		
General population distribution[a]			
IMD 1 (most deprived)	18.3%	21.1%	UK: Love-Koh et al., 2023[16] CA: Lilly 2023[17]
IMD 2	20.2%	19.0%	
IMD 3	20.0%	22.5%	
IMD 4	21.5%	19.5%	
IMD 5 (least deprived)	20.0%	18.0%	
Eligible treatment population distribution[a]			
IMD 1 (most deprived)	37.0%	38.6%	UK: Udeze 2025[18] CA: Lilly 2023[17]
IMD 2	35.4%	23.4%	
IMD 3	17.0%	21.3%	
IMD 4	7.3%	12.1%	
IMD 5 (least deprived)	3.4%	4.7%	

CA, Canada; **IMD**, index of multiple deprivations; **ONS**, Office of National Statistics; **UK**, United Kingdom.

[a] In Canada, IMD quintiles were derived from income quintiles.

RESULTS

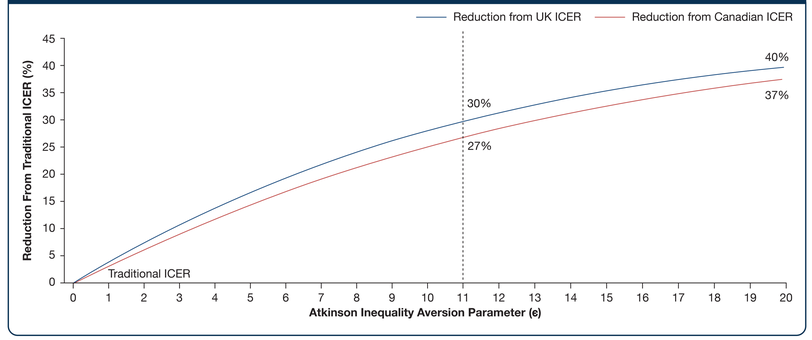
- Compared to treatment with SOC, adoption of exa-cel was associated with an increase in survival of over two decades in both the UK (28.4 years) and Canada (24.6 years)
- Additionally, in the traditional CEA analysis, patients treated with exa-cel experienced an increase in QALYS (+28.5 in the UK, +27.9 in Canada) and a decrease in disease-related costs, including VOC and complication management costs, compared to patients treated with SOC
- The breakdown of net health benefit by IMD quintile shows that exa-cel provides an increasing benefit when moving from less to more deprived groups (-13,436 for IMD 5 vs -2,683 for IMD 1 in the UK, -7,343 vs -1,290 for the same groups in Canada) (**Table 2**)
- The change in SII due to the adoption of exa-cel was found to be -72,075 in the UK and -38,934 in Canada, both of which represent a significant reduction in inequality across the population
- The equity-weighted ICER in both the UK and Canada for exa-cel versus SOC was found to ~30% lower than the traditional ICER, highlighting the effect of accounting for equity-weighting
- **Figure 3** displays the change in the equity-weighted ICER as the Atkinson inequality aversion parameter was varied from 0 (traditional CEA output) to 20. The minimal change in the equity-weighted ICER across the tested values, indicates that the conclusions hold across various assumed values for the decision maker's willingness to accept lesser net health benefits for a decrease in health inequality

Table 2. DCEA Model Results

	UK	Canada
Net health benefit		
IMD 1 (most deprived)	-2,683	-1,290
IMD 2	-3,199	-4,004
IMD 3	-9,077	-4,379
IMD 4	-12,203	-6,007
IMD 5 (least deprived)	-13,436	-7,343
Total	-40,599	-23,023
Change in SII	-72,075	-38,934

IMD, index of multiple deprivations; **SII**, slope index of inequality; **UK**, United Kingdom.

Figure 3. Reduction in Traditional ICER by Atkinson Inequality Aversion Parameter



ICER, incremental cost-effectiveness ratio; **UK**, United Kingdom.

LIMITATIONS

- IMD quintiles measure the deprivation of a geographic area, not explicitly the people living in that area, and thus some patients may have been assigned an IMD group that does not perfectly match their deprivation status
- While SCD-related health inequality is connected with inequalities already experienced by patients of ethnicities more likely to suffer from SCD, IMD measurements do not capture patient ethnicity and are instead being used as a proxy in this analysis
- More recent country-specific inequality aversion parameters were not readily available in the literature

DISCUSSION

- HTA decision making plays a key role on displacement of resources and investment in new health technologies
- Evolution of HTA frameworks is key to encompass the development of new highly innovative technologies in areas with high unmet need to ensure they can reach underserved populations
- The DCEA applied in the recent appraisals of exa-cel is the first successful quantitative approach presented in decision making and is bringing evolution and innovation into HTA decision making
- The case study of exa-cel for the treatment of patients with SCD with VOCs in the UK and Canada provides a definitive example of the impact of innovation in HTA methodology on patient access, incorporating important value elements in current value assessment frameworks

CONCLUSIONS

- **Incorporating the impact of treatment adoption on health inequalities into HTA decision making more accurately reflects the value of highly innovative therapies like exa-cel while also providing HTA bodies with a quantitative means to address these important issues through their assessment processes**

References

1. Hassell KL. *Am J Prev Med*. 2010;38(4 Suppl):S512-21.
2. Kato GJ, et al. *Nat Rev Dis Primers*. 2018;4:18010.
3. Ware RE, et al. *Lancet*. 2017;390:311-23.
4. Sickle Cell Society. No One's Listening - A Report. 2021.
5. Boateng-Kuffour A, et al. Quality of Care and Perceived Barriers to Healthcare: A Comparative Cohort Assessment Among Individuals With Sickle Cell Disease With Recurrent Vaso-occlusive Crises [Oral presentation]. International Society for Quality of Life Research, Calgary, Alberta, Canada; Oct. 18-21, 2023.
6. Frangoul H, et al. *N Engl J Med*. 2024;390:1649-1662.
7. MHRA authorises world-first gene therapy that aims to cure sickle-cell disease and transfusion-dependent β-thalassemia. GOV.UK. Accessed February 19, 2025. https://www.gov.uk/government/news/mhra-authorises-world-first-gene-therapy-that-aims-to-cure-sickle-cell-disease-and-transfusion-dependent-thalassemia.
8. NICE approves groundbreaking one-off gene therapy for severe sickle cell disease. NICE website: The National Institute for Health and Care Excellence. Accessed February 19, 2025. https://www.nice.org.uk/news/articles/nice-approves-groundbreaking-one-off-gene-therapy-for-severe-sickle-cell-disease.
9. Exagamglogene Autotemcel (Casgevy). *Canadian Journal of Health Technologies*. 2025;5:1-35.
10. Lopez A, et al. Model-Projected Long-Term Clinical Outcomes of Exagamglogene Autotemcel (Exa-cel) Gene-Edited Therapy in Patients With Sickle Cell Disease With Recurrent Vaso-Occlusive Crises in the United Kingdom [Poster presentation]. ISPOR Europe, Copenhagen, Denmark; Nov. 12-15, 2023.
11. Udeze C, et al. 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 [Poster presentation]. ISPOR Europe, Barcelona, Spain; Nov. 17-20, 2024.
12. McLennan D. The English Indices of Deprivation 2019, Ministry of Housing, Communities, and Local Government; 2019.
13. Distributional Cost-Effectiveness Analysis: Quantifying Health Equity Impacts and Trade-Offs. Oxford University Press; 2020.
14. Robson M, et al. *Health Econ*. 2017;26:1328-34.
15. Data on File. Vertex Pharmaceuticals Incorporated; 2023.
16. Love-Koh J, et al. *Pharmacoeconomics*. 2023;41:831-41.
17. Lilly L, et al. Healthcare Resource Utilization Among Patients With Sickle Cell Disease With Recurrent Vaso-Occlusive Crises in Canada [Poster presentation]. ISPOR, Atlanta, GA, United States; May 5-8, 2023.
18. Udeze C, et al. *Clinical Therapeutics*. 2025;47:29-36.
19. Office for National Statistics (ONS), ONS website, statistical bulletin. Population estimates for the UK, England, Wales, Scotland and Northern Ireland: mid-2021. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/latest#population-of-england-and-wales
20. Statistics Canada. Population estimates, quarterly. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000901

Disclosures

GV-H, **MG**, **AL**, and **CU** are employees of Vertex Pharmaceuticals Incorporated and may hold stock or stock options in the company.
JS is an employee of Cogentia Healthcare Consulting.

Acknowledgments

The study was supported by Vertex Pharmaceuticals Incorporated. Editorial coordination and support under the guidance of authors was provided by Ciara Silverman and Lorilei Richardson, of Vertex Pharmaceuticals Incorporated, and by Cindi A. Hoover, PhD, of ApotheCom, funded by Vertex Pharmaceuticals Incorporated.