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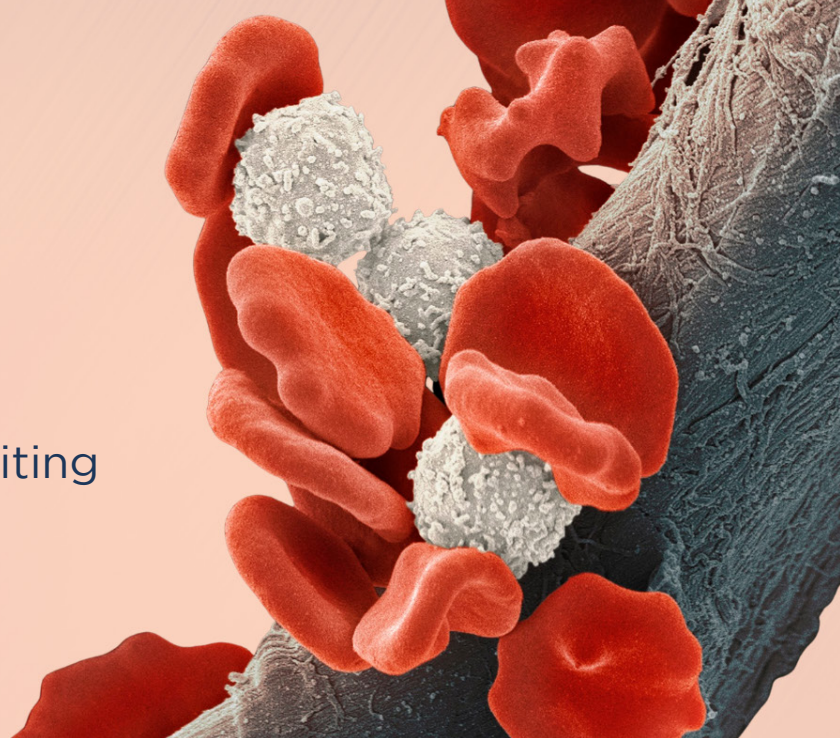

CRISPR-Cas9:

Shaping the Future of Gene Editing in Treating Sickle Cell Disease

TRENDING TOPICS

This month, on the 13th of February 2024, the European Union granted conditional marketing authorisation to CASGEVY™ (exagamglogene autotemcel [exa-cel]), a **CRISPR/Cas9** gene edited therapy. CASGEVY™ is approved for the treatment of patients who are 12 years of age and older with severe sickle cell disease (SCD) characterized by recurrent vaso-occlusive crises (VOCs) or transfusion-dependent beta thalassemia (TDT), for whom hematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen matched related HSC donor is not available. This EU approval along with the Medicines and Healthcare products Regulatory Agency (MHRA) 16th November 2023 conditional marketing authorization and the 8th of December 2023 U.S. Food and Drug Administration approval for CASGEVY™ marks a significant milestone in use of CRISPR/Cas9 to discover and develop potential new treatments aimed at the underlying genetic causes of human disease.

CRISPR, an acronym for **Clustered Regularly Interspaced Short Palindromic Repeats**, is a revolutionary gene-editing technology that allows for precise and efficient alteration of DNA within organisms. It utilizes a system derived from the natural defense mechanisms of bacteria, which capture snippets of DNA from invading viruses and use them to create DNA segments known as CRISPR arrays. CRISPR, in combination with the enzyme Cas9, can be programmed to target specific sequences in the genome. When directed to a specific DNA sequence, Cas9 can cut the DNA at that precise location, enabling the deletion, insertion, or alteration of specific DNA segments, thereby offering unprecedented control in gene editing.

SCD is a debilitating, progressive, life shortening genetic disease. SCD patients report health-related quality of life scores well below the general population and significant health care resource utilization. SCD affects the red blood cells, which are essential for carrying oxygen to all organs and tissues of the body. SCD causes severe pain, organ damage and shortened life span due to misshapen or “sickled” red blood cells. The clinical hallmark of SCD is vaso-occlusive crises (VOCs), which are caused by blockages of blood vessels by sickled red blood cells and result in severe and debilitating pain that can happen anywhere in the body at any time.

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SCD requires lifelong treatment and significant use of health care resources, and ultimately results in reduced life expectancy, decreased quality of life and reduced lifetime earnings and productivity. In Europe, the mean age of death for patients living with SCD is around 40 years. Stem cell transplant from a matched donor is a curative option but is only available to a small fraction of people living with SCD because of the lack of available donors.[1]

Transfusion-Dependent Beta Thalassemia (TDT) is a serious, life-threatening genetic disease. TDT patients report health-related quality of life scores below the general population and significant health care resource utilization. TDT requires frequent blood transfusions and iron chelation therapy throughout a person's life. Due to anemia, patients living with TDT may experience fatigue and shortness of breath, and infants may develop failure to thrive, jaundice and feeding problems. Complications of TDT can also include an enlarged spleen, liver and/or heart, misshapen bones and delayed puberty. TDT requires lifelong treatment and significant use of health care resources, and ultimately results in reduced life expectancy, decreased quality of life and reduced lifetime earnings and productivity. In Europe, the mean age of death for patients living with TDT is 50-55 years. Stem cell transplant from a matched donor is a curative option but is only available to a small fraction of people living with TDT because of the lack of available donors.[1]

Figure 1 - CASGEVY™ FDA Approval Journey

October 2015
Vertex and CRISPR embark on strategic research partnership

January 2019
Fast Track Designation granted for Sickle Cell Disease (SCD)

May 2020
RMAT Designation obtained for SCD and transfusion-dependent beta-thalassemia

July 2022
New data on expanded cohort presented

June 2023
BLA for severe SCD and TDB submitted

October 2023
Advisory committee concludes for exa-cel for severe SCD

December 2023
First ever FDA approval follows MHRA approval for CRISPR based gene editing therapy

Future
Rare paediatric disease priority review voucher provided to Vertex. A postmarketing, prospective, multicenter observational study to assess and characterize the risks of secondary malignancies and off-target effects, and to assess the long-term safety of exagamglogene autotemcel. The study will include 250 subjects with SCD and will be followed for 15 years after product administration.

There are an estimated 2,000 patients eligible for CASGEVY™ in the U.K. and more than 8,000 patients potentially eligible for treatment in the EU alone. However, considering SCD predominates in Africa, it's important to evaluate the impact of these approvals in the context of global data.

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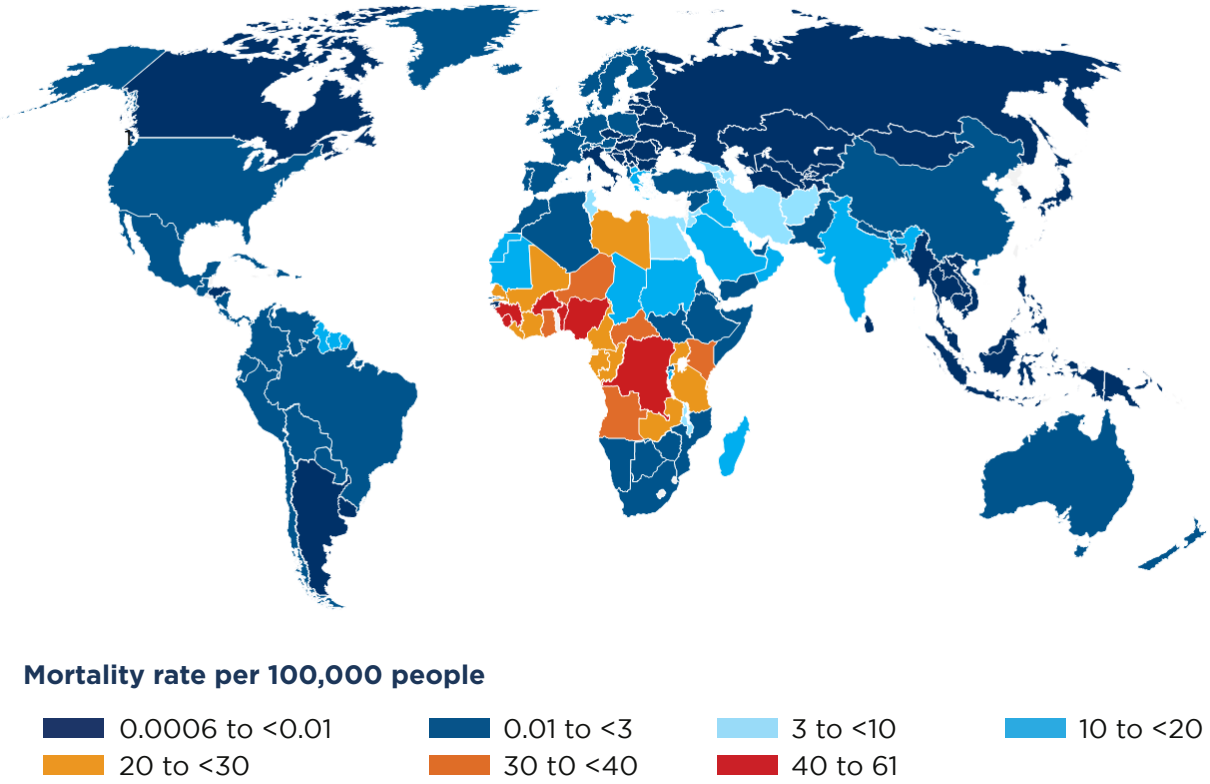
Between 2000 and 2021, national incidence rates of sickle cell disease were relatively stable, but total births of babies with sickle cell disease increased globally by 13·7% (95% uncertainty interval 11·1–16·5), to 515 000 (425 000–614 000), primarily due to population growth in the Caribbean and western and central sub-Saharan Africa. The number of people living with sickle cell disease globally increased by 41·4% (38·3–44·9), from 5·46 million (4·62–6·45) in 2000 to 7·74 million (6·51–9·2) in 2021. It was estimated 34 400 (25 000–45 200) cause-specific all-age deaths globally in 2021, but total sickle cell disease mortality burden was nearly 11-times higher at 376 000 (303 000–467 000). In children younger than 5 years, there were 81 100 (58 800–108 000) deaths, ranking total sickle cell disease mortality as 12th (compared to 40th for cause-specific sickle cell disease mortality) across all causes estimated by the Global Burden of Diseases, Injuries, and Risk Factors Study in 2021.[2]

Figure 2[2] - All-age total sickle cell disease mortality among males and females combined in 2021



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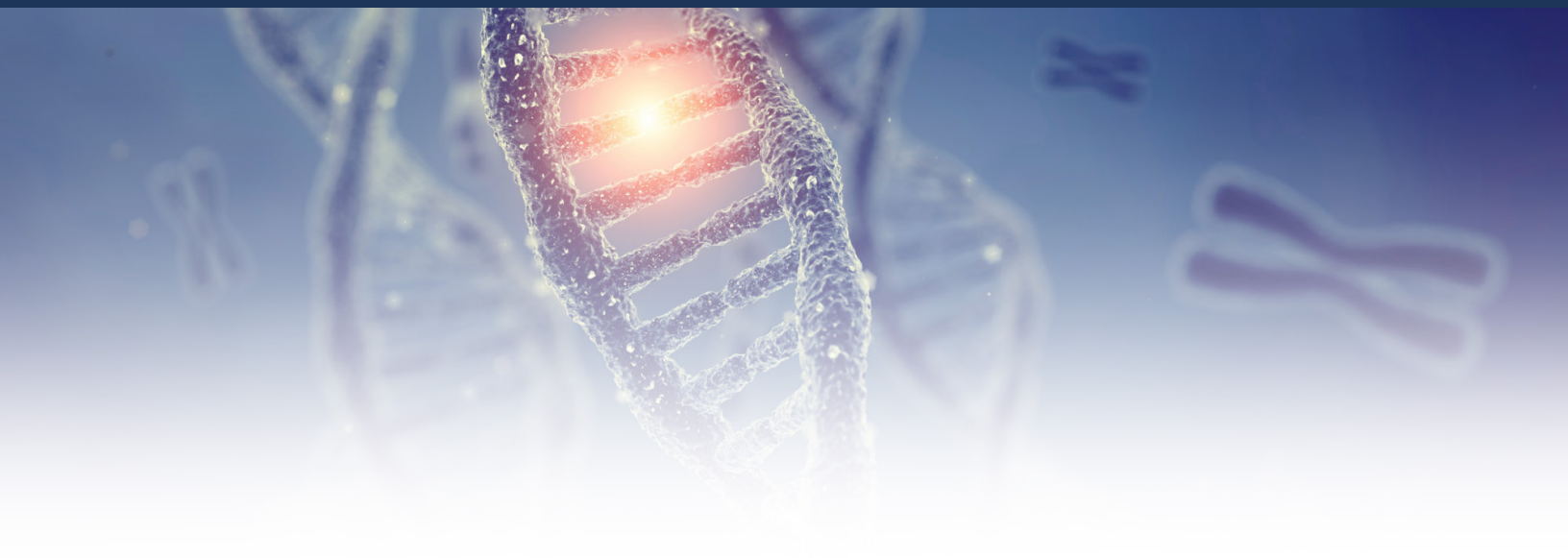

On 08 December 2023 the FDA also approved a second gene therapy for SCD, BlueBird Bio's LYFGENIA™. LYFGENIA™ is a cell-based gene therapy. LYFGENIA™ uses a lentiviral vector (gene delivery vehicle) for genetic modification and is approved for the treatment of patients 12 years of age and older with sickle cell disease and a history of vaso-occlusive events. With LYFGENIA™, the patient's blood stem cells are genetically modified to produce HbAT87Q, a gene-therapy derived hemoglobin that functions similarly to hemoglobin A, which is the normal adult hemoglobin produced in persons not affected by sickle cell disease. Red blood cells containing HbAT87Q have a lower risk of sickling and occluding blood flow. These modified stem cells are then delivered to the patient.
The costs are not clear, but estimates suggest that the price for CASGEVY™ will be $2 million per patient and LYFGENIA™ as much as $3.2 million per patient. In August 2023, the Institute for Clinical and Economic Review (ICER) published a final evidence report on gene therapies for SCD, which modelled each therapy compared with standard of care over a lifetime horizon. ICER assumed identical efficacy for the two therapies given the small number of people studied.

The Health Benefit Price Benchmark (HBPB) for treatment with either lovo-cel (LYFGENIA™) or exa-cel (CASGEVY™) ranges from $1,350,000 to $2,050,000, with recommendations that pricing be at the lower end of the range. "Although uncertainties about durability and harm remain, both lovo-cel and exa-cel are likely to substantially improve quality and length of life among patients with SCD. Ultimately, cost effectiveness will depend on the actual prices for these therapies".[3]

With cost estimates as high as this, one could question the ability to make meaningful impact to the growing number of individuals living with SCD, or the increasing total SCD mortality burden in countries outside of the big markets. Though high burden countries have established a sickle cell disease unit in their ministries of health, very few have allocated annual budget funds for health promotion of sickle cell disease, and even less have allocated funding for newborn screening.

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Though companies like Vertex (Vertex and CRISPR Therapeutics entered into a strategic research collaboration in 2015 focused on the use of CRISPR/Cas9 to discover and develop potential new treatments aimed at the underlying genetic causes of human disease) are already working closely with national health authorities to secure access for eligible patients as quickly as possible, marked progress in improving SCD outcomes requires global action, including efficient diagnostic screening, effective case monitoring through population registries, and implementation of high-quality prevention and treatment.

Since 2019, the FDA has awarded 43 total review designations to 21 distinct CRISPR treatments. Over this period, the orphan drug designation has been awarded 22 times, and the fast-track designation, ten. The newly approved CASGEVY™ stands out as the leader, having secured seven designations.[4] GlobalData estimates that by 2029, CRISPR drugs will generate more than $7 billion annually, therefore ongoing evaluation to support fair pricing, ensuring access to the most underrepresented populations and markets, and implementing global PV systems to collect and monitor unfamiliar adverse events over prolonged periods will be required.

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References

1 Vertex. (2024, February 13). European Commission Approves First CRISPR/Cas9 Gene-Edited Therapy, CASGEVY™ (exagamglogene autotemcel), for the Treatment of Sickle Cell Disease and Transfusion-Dependent Beta Thalassemia [Press release].

2 Thomson, A. M. (2023). Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000–2021: a systematic analysis from the Global Burden of Disease Study 2021. The Lancet Haematology

3 Institute for Clinical and Economic Review. (2023). 2023 Final Evidence Report – Gene Therapies for Sickle Cell Disease.

4 Global Data. (2024, January 31). FDA awarded record number of review designations to CRISPR drugs in 2023 [Report].