# FDA Approves Two Sickle Cell Gene Therapies, But They Are Not Identical

*By Robert Kordella, RPh*

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# On Friday, December 8, the FDA approved two cell-based gene editing therapies

for the treatment of sickle cell disease (SCD): Vertex and CRISPR Therapeutics' CASGEVY (exagamglogene autotemcel) and bluebird bio's LYFGENIA (lovotibeglogene autotemcel).

SCD affects approximately 100,000 people in the U.S., causing red blood cells (RBCs) to deform into a characteristic "sickle" shape, resulting in those cells' inability to travel smoothly through small blood vessels and capillaries throughout the body. These disruptions in smooth blood flow produce vaso-occlusive crises (VOCs), which are painful manifestations of this inability of RBCs to flow smoothly. Organs, joints and everywhere that blood flows in the body can potentially be the site of a painful and dangerous VOC. Depending on their severity and location, VOCs can be fatal. VOCs result in high rates of ED visits, hospitalization, illness and early death. The average lifespan of a patient suffering from SCD is 54 years. African Americans are disproportionately impacted by SCD, with an incidence of ~1 in 365 live births.

The following table outlines some of the similarities between Casgevy and Lyfgenia.

## SIMILARITIES BETWEEN CASGEVY AND LYFGENIA

| | CASGEVY | LYFGENIA |
|---|---|---|
| FDA Approval Language | Approved for the treatment of SCD in patients 12 years of age and older with recurrent VOCs | Approved for the treatment of patients 12 years of age and older with SCD and a history of VOCs |
| Myeloablative pre-treatment required? | Yes. | |
| Administration | One-time IV reinfusion of patient's own genetically modified bone marrow cells. | |
| Long-term safety and effectiveness monitoring required? | Yes. | |

| | CASGEVY | LYFGENIA |
|---|---|---|
| Limited number of treatment centers across the country? 1 | Yes. | |
| Treatment occurs over the course of several months. | Yes. | |
| Cost impact primarily to medical benefit vs. pharmacy benefit | Yes. | |
| Special FDA designations | Orphan Drug, Fast Track, Regenerative Medicine Advanced Therapy, Rare Pediatric Disease. | Orphan Drug, Fast Track |

Myeloablative pre-treatment refers to the process, similar to that used in a traditional bone marrow transplant, in which high doses of a chemotherapy agent, busulfan, are used to wipe out the patient's own faulty bone marrow cells responsible for making sickled RBCs, prior to the reinfusion of the patient's own bone marrow cells that will have been genetically modified to produce typically shaped RBCs.

The following table will quickly highlight some of the key differences between Casgevy and Lyfgenia.

## DIFFERENCES BETWEEN CASGEVY AND LYFGENIA

| | CASGEVY | LYFGENIA |
|---|---|---|
| Technology | CRISPR/Cas9 editing. | Lentiviral vector. |
| Clinical trial results | 93.5% (29 of 31) of evaluable patients achieved freedom from severe VOC episodes for at least 12 consecutive months during the 24-month follow-up period. All treated patients achieved successful engraftment and no patients experienced graft failure or graft rejection, nor were any safety signals observed. | 87.5% (28 of 32) of evaluable patients achieved complete resolution of vaso-occlusive events (VOE-CR) between 6–8 months following infusion. |
| FDA Black Box Warning | No. | Yes, due to hematologic malignancies – lifelong monitoring for leukemia, lymphoma, myeloma, etc. is required. |
| Institute for Clinical and Economic Review (ICER) Cost-Effectiveness Threshold | Cost-effective at price up to $2.05 million vs. standard of care including drug treatment for VOCs, transfusions, hospitalizations, and other supportive care. | |
| Price | $2.2 million | $3.1 million |

A Black Box Warning is the highest level of cautionary alert that the FDA can provide to a drug that it deems worthy of approval, nonetheless. It requires a heightened level of attentive monitoring by prescribers and care teams to known or suspected consequences.

The ICER cost-effectiveness threshold is a complex algorithm that assesses the clinical and economic impact of a treatment vs. the standard of care over a defined time period. Treatments priced at or below the ICER Cost-

Effectiveness Threshold are deemed by ICER to be "cost-effective" from a societal point-of- view. In this case Casgevy meets the ICER threshold, Lyfgenia does not.

Casgevy is also being assessed by the FDA for the treatment of transfusion-dependent beta thalassemia with an expected decision date of note later than March 30,2024.

Please note that Casgevy requires specialized experience in stem cell transplantation and is currently approved for administration at the following authorized treatment centers:

- Boston Medical Center (Boston, MA)
- Children's National Hospital (Washington, D.C.)
- City of Hope Children's Cancer Center (Los Angeles, CA)
- Medical City Children's Hospital (Dallas, TX)
- Methodist Children's Hospital (San Antonio, TX)
- Nationwide Children's Hospital (Columbus, OH)
- The Children's Hospital at TriStar Centennial (Nashville, TN)
- The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (Columbus, OH)
- University of Chicago/Comer Children's Hospital (Chicago, IL)

Additional treatment centers will be authorized to administer Casgevy in the near future.

While the news of these therapies continue to develop, feel free to reach out to your Excelsior Solutions team with any questions or concerns.