Casgevy™ (exagamglogene autotemcel) and Lyfgenia® (lovotibeglogene autotemcel) – New orphan drug approvals

- On December 8, 2023, the FDA announced the approval of two gene therapies for sickle cell disease (SCD): Vertex's Casgevy (exagamglogene autotemcel) and bluebird bio's Lyfgenia (lovotibeglogene autotemcel).
    - Casgevy is approved for the treatment of SCD in patients 12 years and older with recurrent vaso-occlusive crises (VOCs).
    - Lyfgenia is approved for the treatment of SCD in patients 12 years and older with a history of vaso-occlusive events (VOEs).
- SCD is an inherited blood disorder affecting approximately 100,000 people in the U.S. It is most common in African Americans. The primary problem in SCD is a mutation in hemoglobin. This mutation causes red blood cells to develop a crescent or "sickle" shape. These sickled red blood cells restrict the flow in blood vessels and limit oxygen delivery to the body's tissues, leading to severe pain and organ damage called VOEs or VOCs. The recurrence of these events or crises can lead to life-threatening disabilities and/or early death.
- Casgevy is the first FDA-approved therapy utilizing CRISPR/Cas9, a type of genome editing technology. Patients' hematopoietic (blood) stem cells are modified by genome editing using CRISPR/Cas9 technology.
    - CRISPR/Cas9 can be directed to cut DNA in targeted areas, enabling the ability to accurately edit DNA where it was cut. The modified blood stem cells are transplanted back into the patient where they engraft within the bone marrow and increase the production of fetal hemoglobin (HbF). In patients with SCD, increased levels of HbF prevent the sickling of red blood cells.
- Lyfgenia uses a lentiviral vector for genetic modification. With Lyfgenia, the patient's blood stem cells are genetically modified to produce HbA^{T87Q}, a gene-therapy derived hemoglobin that functions similarly to hemoglobin A, which is the normal adult hemoglobin produced in persons not affected by SCD. Red blood cells containing HbA^{T87Q} have a lower risk of sickling and occluding blood flow. These modified stem cells are then delivered to the patient.
- Both products are made from the patients' own blood stem cells, which are modified, and are given back as a one-time, single-dose infusion as part of a hematopoietic stem cell transplant. Prior to treatment, a patients' own stem cells are collected, and then the patient must undergo myeloablative conditioning.
- The efficacy of Casgevy was established in a single-arm study in patients with SCD. A total of 31 patients were included in the evaluation of the primary endpoint. The primary outcome was the proportion of VF12 responders, defined as patients who did not experience any protocol-defined severe VOCs for at least 12 consecutive months within the first 24 months after Casgevy infusion.
    - The VF12 response rate was 29/31 (93.5%, 98% one-sided CI: 77.9, 100.0).
- The efficacy of Lyfgenia was established in a single-arm study in patients with SCD. A total of 32 patients were included in the evaluation of the primary endpoint. The primary outcomes were the

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complete resolution of VOEs (VOE-CR) and severe VOEs (sVOE-CR) between 6 months and 18 months after infusion of Lyfgenia.

  - The VOE-CR response rate was 28/32 (88%, 95% CI: 71, 97).
  - The sVOE-CR response rate was 30/32 (94%, 95% CI: 79, 99).

- Lyfgenia carries a boxed warning for hematologic malignancy.
- Additional warnings and precautions for Lyfgenia include delayed platelet engraftment; neutrophil engraftment failure; insertional oncogenesis; hypersensitivity reactions; anti-retroviral use; hydroxyurea use; iron chelation; and interference with PCR-based testing.
- Warnings and precautions for Casgevy include potential neutrophil engraftment failure; prolonged time to platelet engraftment; hypersensitivity reactions; and off-target genome editing risk.
- The most common grade 3 or 4 non-laboratory adverse reactions (≥ 25%) with Casgevy use were mucositis, febrile neutropenia, and decreased appetite. The most common grade 3 or 4 laboratory abnormalities (≥ 50%) were neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia.
- The most common adverse reactions ≥ grade 3 (≥ 20%) with Lyfgenia use were stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia.
- The minimum recommended dose of Casgevy and Lyfgenia is 3×10^6 CD34+ cells/kg. Both are administered as a one-time single-dose intravenous infusion.
- The wholesale acquisition cost (WAC) of Casgevy and Lyfgenia is expected to be $2.2 million and $3.1 million, respectively.
- Lyfgenia will be available through bluebird's established national network of Qualified Treatment Centers beginning in 1Q 2024.
- Vertex's launch plans for Casgevy are pending.