U.S. FOOD & DRUG ADMINISTRATION

Regulatory Considerations CBER

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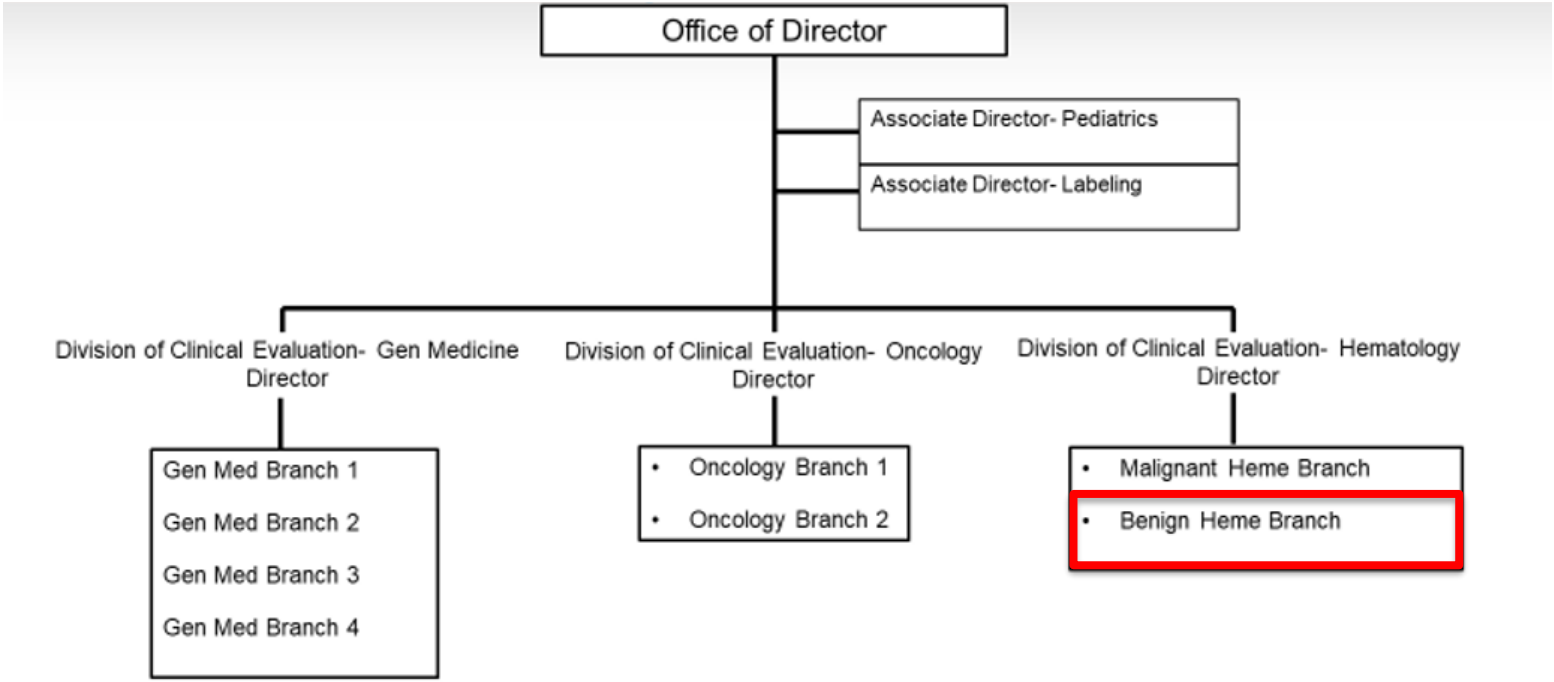
Office of Clinical Evaluation
Super Office of Therapeutic Products
Center for Biologics Evaluation and Research



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Editorial

Gene therapy: The ultimate cure for hereditary diseases

THE OFFICIAL JOURNAL OF THE ROYAL PHARMACEUTICAL SOCIETY

the PHARMACEUTICAL JOURNAL

Advanced therapy medicinal products

13 January 2022

By **Rachel Brazil**

Gene therapy: from catastrophe to cure in 20 years

After several setbacks since its inception over 30 years ago, *in vivo* gene therapy is starting to make some significant headway, with new therapies being developed across various therapeutic areas, from ophthalmology to oncology.

FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease

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For Immediate Release: December 08, 2023

Today, the U.S. Food and Drug Administration approved two milestone treatments, Casgevy and Lyfgenia, representing the first cell-based gene therapies for the treatment of sickle cell disease (SCD) in patients 12 years and older. Additionally, one of these therapies, Casgevy, is the first FDA-approved treatment to utilize a type of novel genome editing technology, signaling an innovative advancement in the field of gene therapy.

Sickle cell disease is a group of inherited blood disorders affecting approximately 100,000 people in the U.S. It is most common in African Americans and, while less prevalent, also affects Hispanic Americans. The primary problem in sickle cell disease is a mutation in hemoglobin, a protein found in red blood cells that delivers oxygen to the body's tissues. 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 vaso-occlusive events (VOEs) or vaso-occlusive crises (VOCs). The recurrence of these events or crises can lead to life-

https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapies-treat-patients-sickle-cell-disease

Licensed Products

- CASGEVY (exagamglogene autotemcel) – For the treatment of patients aged 12 years and older with sickle cell disease (SCD) with recurrent vaso occlusive crises (VOCs) and transfusion-dependent ß-thalassemia (TDT)
- LYFGENIA (lovotibeglogene autotemcel) – For the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events (VOEs)
- ZYNTEGLO (betibeglogene autotemcel) – For the treatment of adult and pediatric patients with ß-thalassemia who require regular red blood cell (RBC) transfusions

Cellular and Gene Therapy Approved Products

https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

The New York Times

First Patient Begins Newly Approved Sickle Cell Gene Therapy

A 12-year-old boy in the Washington, D.C., area faces months of procedures to remedy his disease. "I want to be cured," he said.

First Patient Begins Sickle Cell Gene Therapy That F.D.A. Approved - The New York Times (nytimes.com)

Regulatory Considerations

- Variability in patient course of disease
  - Enrollment criteria
- Selecting an appropriate outcome measure
  - Clinically meaningful benefit
  - Pain (vaso-occlusive crises/events), organ function, surrogate markers
- Durability of response

Regulatory Considerations

- Type of product
  - LVV vs Gene editing/CRISPR
- Risk tolerance for gene therapy/gene editing
- Short term safety
  - Platelet and Neutrophil Recovery
- Long term safety
  - Need for ongoing long-term patient follow up

Boxed Warning and Patient Medication Guide

WARNING: HEMATOLOGIC MALIGNANCY

See full prescribing information for complete boxed warning.

Hematologic malignancy has occurred in patients treated with LYFGENIA. Monitor patients closely for evidence of malignancy through complete blood counts at least every 6 months and through integration site analysis at Months 6, 12, and as warranted. (5.1)

Post-Marketing Long Term Follow-Up Study

Patients who intend to receive treatment with LYFGENIA are encouraged to enroll in the study, as available, to assess the long-term safety of LYFGENIA and the risk of malignancies occurring after treatment with LYFGENIA by calling bluebird bio at 1-833-999-6378. The study includes monitoring (at pre-specified intervals) for clonal expansion.

MEDICATION GUIDE

LYFGENIA® (pronounced lif-*JEN*-ee-*uh*)

(lovotibeglogene autotemcel)

What is the most important information I should know about LYFGENIA?

Patients treated with LYFGENIA have developed blood cancers. Treatment with LYFGENIA may increase your risk of developing blood cancer. Blood cancer can develop many years after treatment with LYFGENIA. Blood cancer can be life-threatening and/or cause death.

Because of the risk of blood cancer, you should talk to your doctor about the benefits and risks of LYFGENIA, and about your treatment options. Your doctor may evaluate if you have risk factors that increase your chances of developing blood cancer after LYFGENIA.

Because of the risk of cancer, it is important for you to be monitored at least every 6 months for a minimum of 15 years after LYFGENIA. Monitoring will include blood tests that measure your blood cell counts and evaluation of the blood cells where the gene product is present with specialized tests. If these tests are abnormal, additional testing may be recommended by your doctor. Additional testing might include more frequent blood tests to watch you more closely for changes in your blood. Additional testing could also include a bone marrow evaluation, which can tell your doctor if a blood cancer is developing.

Blood cancer may cause no symptoms, or symptoms can be general. You or your caregiver should call your healthcare provider right away for any of these signs or symptoms:

- Abnormal bruising or bleeding (including nosebleed)
- Blood in urine, stool, or vomit
- Coughing up blood
- Severe headache
- Unusual stomach or back pain
- Fever (100.4°F/38°C or higher)
- Swollen glands
- Abnormal tiredness

If you are diagnosed with a cancer, have your treating physician contact bluebird bio at 1-833-999-6378.

Long Term Follow-Up After Administration of Human Gene Therapy Products

Guidance for Industry

Long Term Follow-up After Administration of Human Gene Therapy Products | FDA

Human Gene Therapy Products Incorporating Human Genome Editing

Guidance for Industry

Human Gene Therapy Products Incorporating Human Genome Editing | FDA

Summary

- Overall Benefit-Risk Assessment
- FDA may require postmarketing studies
- Our goal to ensure safe and effective products in the U.S. population

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  Email: OTPRPMS@fda.hhs.gov
- **Interactions with Office of Therapeutic Products website:**

  Interactions with Office of Therapeutic Products | FDA
- **OTP Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

FDA Headquarters

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch**: ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch**: industry.biologics@fda.hhs.gov
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