CASGEVY®
MANUFACTURING AND QUALITY

casgevy® (exagamglogene autotemcel) suspension for IV infusion

An overview of the key steps involved in the 5- to 6-month process for CASGEVY manufacturing and quality testing

INDICATION

CASGEVY is indicated for the treatment of patients aged 12 years and older with:
- sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs)
- transfusion-dependent β-thalassemia (TDT)

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Neutrophil Engraftment Failure
There is potential risk of neutrophil engraftment failure after treatment with CASGEVY. In the clinical trials, all treated patients achieved neutrophil engraftment and no patients received rescue CD34+ cells.

Monitor absolute neutrophil counts (ANC) and manage infections according to standard guidelines and medical judgement. In the event of neutrophil engraftment failure, patients should be infused with rescue CD34+ cells.

Please see additional Important Safety Information below.

Cell collection

- After it is determined that your patient is appropriate for CASGEVY and has completed pre-mobilization, they will be required to undergo mobilization followed by apheresis at an Authorized Treatment Center (ATC) to collect as many CD34+ hematopoietic stem cells (HSCs) as possible for CASGEVY manufacturing[1,2]

Cell transportation

- Following apheresis, the collected CD34+ cells are immediately stored and maintained at 2-8 °C in a sterile collection bag and transported to the Vertex manufacturing site. Cells are shipped at the end of Day 1 and Day 2 of collection[2,3]
- A GPS tracker allows the cells to be monitored as they are transported via courier[2]

As an autologous treatment, CASGEVY utilizes your patient's own HSCs.[1] Rigorous chain of identity and custody procedures are employed during each step of manufacturing and quality testing to ensure your patient receives their edited cells back for infusion.[2]

Gene editing

- Following strict sterilization procedures, the collected HSCs are enriched for CD34+ cells[3,4]
- These cells undergo electroporation, which uses an electric pulse to create temporary pores within the cell membrane[3]
- This process enables entry of the CRISPR/Cas9 complex into the CD34+ cells, facilitating targeted gene editing at a precise location within the genome[3]
- The entire gene-editing process takes approximately 6 days[3]

Although off-target genome editing was not observed in the edited CD34+ cells evaluated from healthy donors and patients, the risk of unintended, off-target editing in an individual's CD34+ cells cannot be ruled out due to genetic variants. The clinical significance of potential off target editing is unknown.[1]

Cell harvest and drug product cryopreservation

- Following electroporation and the editing process, the edited CD34+ cells are suspended in a cryopreservative solution to protect them during the freezing step in a controlled rate freezer, then stored in liquid nitrogen until quality testing has concluded[3]

The cryopreservation process helps maintain the stability of the edited cells.[3]

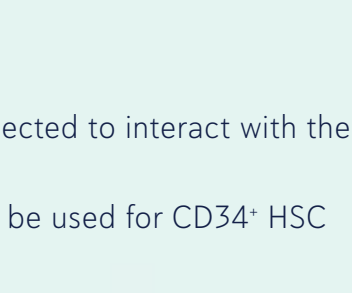
Quality release testing

- While the majority of edited CD34+ cells are frozen, a small sample undergo rigorous testing for **viability, purity, content, potency, sterility, and other safety release tests**[3]
- Innovative, cell-based assays help ensure a high-quality product is delivered. Some assays require cell culture and differentiation, which can take multiple weeks[3]

The gene editing process using CRISPR/Cas9 to make CASGEVY is precise.[1] Quality testing may take up to 5-6 months, as it is an intensive process done to ensure the final product is ready for your patient.[3]

Cell shipment and treatment initiation

- Once quality testing is complete and enough CD34+ cells have been edited to meet the minimum dose, CASGEVY is ready to be shipped back to the ATC for infusion[2,3]



IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Delayed Platelet Engraftment
Delayed platelet engraftment has been observed with CASGEVY treatment. There is an increased risk of bleeding until platelet engraftment is achieved. In the clinical trials, there was no association observed between incidence of bleeding events and time to platelet engraftment.

Monitor patients for bleeding according to standard guidelines and medical judgement. Conduct frequent platelet counts until platelet engraftment and platelet recovery are achieved. Perform blood cell count determination and other appropriate testing whenever clinical symptoms suggestive of bleeding arise.

Hypersensitivity Reactions
Hypersensitivity reactions, including anaphylaxis can occur due to dimethyl sulfoxide (DMSO) or dextran 40 in the cryopreservative solution. Monitor patients for hypersensitivity reactions during and after infusion.

Off-Target Genome Editing Risk
Although off-target genome editing was not observed in the edited CD34+ cells evaluated from healthy donors and patients, the risk of unintended, off-target editing in an individual's CD34+ cells cannot be ruled out due to genetic variants. The clinical significance of potential off-target editing is unknown.

ADVERSE REACTIONS

The most common Grade 3 or 4 non-laboratory adverse reactions (occurring in ≥ 25%) were mucositis and febrile neutropenia in patients with SCD and patients with TDT, and decreased appetite in patients with SCD.

All (100%) of the patients with TDT and SCD experienced Grade 3 or 4 neutropenia and thrombocytopenia. Other common Grade 3 or 4 laboratory abnormalities (≥ 50%) include leukopenia, anemia, and lymphopenia.

DRUG INTERACTIONS

No formal drug interaction studies have been performed. CASGEVY is not expected to interact with the hepatic cytochrome P450 family of enzymes or drug transporters.

Use of Granulocyte-Colony Stimulating Factor (G-CSF): G-CSF must not be used for CD34+ HSC mobilization of patients with SCD.

Use of Hydroxyurea: Discontinue the use of hydroxyurea at least 8 weeks prior to start of each mobilization cycle and conditioning. There is no experience of the use of hydroxyurea after CASGEVY infusion.

Use of Voxelotor and Crizanlizumab: Discontinue the use of voxelotor and crizanlizumab at least 8 weeks prior to start of mobilization and conditioning, as their interaction potential with mobilization and myeloablative conditioning agents is not known.

Use of Iron Chelators: Discontinue the use of iron chelators at least 7 days prior to initiation of myeloablative conditioning, due to potential interaction with the conditioning agent. Some iron chelators are myelosuppressive. If iron chelation is required, avoid the use of non-myelosuppressive iron chelators for at least 3 months and use of myelosuppressive iron chelators for at least 6 months after CASGEVY infusion. Phlebotomy can be used instead of iron chelation, when appropriate.

USE IN SPECIFIC POPULATIONS

Pregnancy/Lactation: CASGEVY must not be administered during pregnancy and breastfeeding should be discontinued during conditioning because of the risks associated with myeloablative conditioning. Pregnancy and breastfeeding after CASGEVY infusion should be discussed with the treating physician.

Females and Males of Reproductive Potential: A negative serum pregnancy test must be confirmed prior to the start of each mobilization cycle and reconfirmed prior to myeloablative conditioning.

Women of childbearing potential and men capable of fathering a child should use effective methods of contraception from start of mobilization through at least 6 months after administration of CASGEVY. Advise patients of the risks associated with conditioning agents.

Infertility has been observed with myeloablative conditioning therefore, advise patients of fertility preservation options before treatment, if appropriate.

Please see full Prescribing Information for CASGEVY.

References: 1. CASGEVY [prescribing information]. Vertex Pharmaceuticals Incorporated. Boston, MA; January 2024. **2.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-17378 (v1.0); 2022. **3.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-18762 (v12.0); 2024. **4.** Protocol for: Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 gene editing for sickle cell disease and β-thalassemia. *N Engl J Med*. 2021;384(3):252-260. doi:10.1056/NEJMoa2031054