

New Drug Evaluation: Gene Therapies for Sickle Cell Disease and Transfusion Dependent Beta Thalassemia

Date of Review: June 2024

Generic Name: Exagamglogene autotemcel (exa-cel)
Lovotibeglogene autotemcel (lovo-cel)

End Date of Literature Search: 04/02/2024

Brand Name (Manufacturer): Casgevy (Vertex)
Lyfgenia (Bluebird)

Dossier Received: yes

Plain Language Summary:

- Sickle cell disease is a life-long condition that occurs when people are born with abnormally-shaped red blood cells. These red blood cells get stuck in blood vessels, block blood flow, and cause pain and organ damage. Severe pain related to sickle cell disease is called a vaso-occlusive crisis.
- Beta thalassemia is a life-long condition that people are born with that occurs when the body does not make enough hemoglobin, resulting in fewer healthy red blood cells. Some people with beta thalassemia must receive blood transfusions. Transfusions are when a person is given blood that came from a donor.
- The Food and Drug Administration approved 2 new medicines, called gene therapies, for people with sickle cell disease and beta thalassemia. These gene therapies are administered as a single lifetime dose. They are designed to help the body make healthy red blood cells on its own. Studies for these treatments had only a small number of people and did not compare them to other medicine. This can make it difficult to understand how well these treatments work and what side effects they may have.
- Exagamglogene autotemcel (CASGEVY) and lovotibeglogene autotemcel (LYFGENIA) are approved for people 12 years and older with sickle cell disease and recurrent vaso-occlusive crises. Data show that people with sickle cell disease who receive this therapy have fewer vaso-occlusive crises than they did before receiving this therapy. We do not know how long these improvements may last; studies are happening now to answer that question.
- The FDA also approved exagamglogene autotemcel (CASGEVY) for people with beta thalassemia who need transfusions. Data show that people with transfusion-dependent beta thalassemia who receive this therapy may no longer need blood transfusions. We do not know how long these improvements may last; studies are happening now to answer that question.
- Most people who received this medicine had side effects. These gene therapies have to be administered with other medicines in order to create healthy red blood cells, and most side effects were because of these other medicines.
- Drug Use Research and Management (DURM) recommends that the Oregon Health Plan only pay for these medicines when a prescriber shows that the medicine is used safely and correctly. This process is called prior authorization.

Research Questions:

1. What is the effectiveness of exagamglogene autotemcel for sickle cell disease (SCD) or transfusion dependent beta thalassemia (TDT)?
2. What are the harms of exagamglogene autotemcel for SCD or TDT?
3. What is the effectiveness of lovotibeglogene autotemcel for sickle cell disease (SCD)?
4. What are the harms of lovotibeglogene autotemcel for SCD?

5. Are there any important subgroups of patients where exagamglogene autotemcel or lovetibeglogene autotemcel has not been studied or may have different effects?

Conclusions:

- There is low quality evidence based on one poor quality, open-label, single-arm, phase 1/2/3 trial in patients 12 to 35 years of age with SCD and recurrent vaso-occlusive crises (VOC) that people who received exagamglogene autotemcel did not experience any severe vaso-occlusive crises (VOC) for at least 12 consecutive months within a 24-month evaluation window (responder rate 29/31; 93.5%; 98% one-sided confidence interval [CI] 77.9 to 100.0%). Prior to treatment, enrolled participants had at least 2 VOC per year (annualized baseline rate 3.5/year).¹⁻⁵ The full trial is ongoing and unpublished.
- There is low quality evidence based on one poor quality, open-label, single-arm, phase 1/2/3 trial in patients 12 to 35 years of age with TDT. After receiving exagamglogene autotemcel, 91.4% of people were transfusion independent for at least 12 consecutive months within a 24-month evaluation window (responder rate 32/35; 91.4%; 98.3% one-sided CI 75.7% to 100%).²⁻⁶ The full trial is ongoing and unpublished.
- There is low quality evidence based on one poor quality, open-label, single-arm, phase 1/2 trial in patients 12 to 50 years of age with SCD and recurrent vaso-occlusive events (VOE) that lovetibeglogene autotemcel reduces vaso-occlusive events. Eighty-eight percent of people receiving lovetibeglogene autotemcel experienced complete resolution of VOE (VOE-CR) from month 6 to month 18 (Response rate 28/32; 88%; 95% CI 71 to 97%).⁷⁻⁹ The full trial is unpublished.
- Serious adverse events occurred in 45% (SCD) and 33% (TDT) of patients in the exagamglogene autotemcel studies. Most were related to myeloablative conditioning.⁵
- Serious adverse events occurred in 73% of patients treated with lovetibeglogene autotemcel. Most were related to myeloablative conditioning and the underlying disease. Lovetibeglogene autotemcel has a box warning for hematologic malignancy requiring integration site analysis at months 6 and 12 and complete blood count (CBC) every 6 months for at least 15 years due to 2 cases of acute myeloid leukemia (AML) and 1 case of myelodysplastic syndrome (MDS) in earlier studies of this medication.⁹
- There is insufficient data to assess efficacy or safety for individual groups of people. Assessment of subgroups was not performed secondary to incomplete data availability.

Recommendations:

- Implement prior authorization to ensure safe and appropriate use of gene therapy for SCD and TDT.
- Maintain exagamglogene autotemcel and lovetibeglogene autotemcel as non-preferred on the Oregon Health Plan (OHP) preferred drug list (PDL).

Background:

Sickle Cell Disease

Sickle cell disease is a common genetic disorder, with an estimated incidence of about 100,000 people in the United States (US).¹⁰ Sickle cell disease is most prevalent in people of African, Mediterranean and Asian descent.¹⁰ Sickle cell disease often presents in toddlers or young children and results in shortened life expectancy.¹¹ The cause of SCD is a genetic mutation of the hemoglobin (Hb) structure that results in red blood cells with a sickle-shape which are inflexible and increase the viscosity of blood.¹² Patients with SCD may either inherit two sickle genes (HbSS genotype) or inherit one sickle cell gene from one parent and different hemoglobin gene from the other parent (e.g., hemoglobin C, β -thalassemia).¹³ The HbSS genotype is the most common genotype, occurring in 60-75% of SCD patients in the US.¹⁴ Both the HbSS and HbS β -thalassemia genotypes are referred to as sickle cell anemia (SCA).¹⁵ Common characteristics of SCD are red blood cell hemolysis, vaso-occlusion, and obstruction of blood flow. The blockage of small blood vessels prevents oxygen delivery to tissues causing severe

pain.¹³ Resulting comorbidities include blood clots, infection, organ damage, retinopathy, stroke and pain in the joint, extremities, back or chest. Standard pharmacological treatment options for SCD are hydroxyurea, l-glutamine, and most recently, crizanlizumab and voxelotor. Hydroxyurea is the most utilized treatment for SCD and works by increasing fetal hemoglobin (HbF) concentrations. Infants are born with high levels of HbF, which gradually decreases with age to a normal adult level of HbF of less than 1% by age 2.¹⁶ Studies have found that increasing levels of HbF help to prevent disorders of beta globin gene expression associated with SCD.¹⁶ Non-pharmacological therapies for SCD include blood transfusions (to increase the oxygen capacity of blood), hemopoietic stem cell transplant and phlebotomy. Phlebotomy aids in reduction of Hemoglobin S polymerization associated with SCD and subsequently decreases hospitalization duration and reduced Hb levels.¹⁷

Clinically meaningful outcomes for SCD include reduction in stroke, sickle cell pain crises, need for blood transfusion, end-organ damage, and mortality. Increases in hemoglobin concentrations are often measured to evaluate medication efficacy; however, specific HbF concentrations have not been correlated with subsequent clinical outcomes.¹¹

Beta Thalassemia

Beta thalassemia is an inherited, genetic blood disorder where there is insufficient production of β -hemoglobin (β^+) or an absence of β -globin (β^0), resulting in decreased production of healthy red blood cells (RBCs). This may result in anemia and based on the severity of phenotype, beta thalassemia can be labeled as TDT or transfusion nondependent. There are different genotypic forms of this disease. Individuals with severe forms of the disease can require regular transfusions of packed RBCs, which can result in iron overload and the need for concomitant iron chelation therapy.¹⁸

A complete blood count is generally required to diagnose beta thalassemia. It is most prevalent in Asia and the Mediterranean basin, but is estimated to have increased 7.5% over the last 50 years in the United States. Migration was considered as an important factor for this higher trend in beta thalassemia prevalence.¹⁸ Global incidence of symptomatic disease is approximately 1 in 100,000 and can vary greatly geographically.¹⁹

Treatment options for TDT include splenectomy, hematopoietic stem cell transplant (HSCT), and FDA-approved drug therapies such as luspatercept. Donor matching, reduced survival rate for adults, and risk of graft versus host disease (GVHD) are concerns when HSCT is used to treat people with beta thalassemia.¹⁸ While HSCT is potentially curative, it is generally most successful in younger children with a human leukocyte antigen (HLA)-identical sibling donor.²⁰ The Food and Drug Administration (FDA) approved the first gene therapy for beta thalassemia in the form of betibeglogene autotemcel in August 2022.²¹ Outcomes used when caring for patients with TDT or researching interventions include hemoglobin levels, frequency of transfusions, fatigue, and Quality of Life (QoL) assessments.¹⁸ There are no clear minimum clinically important differences (MCID) for these outcomes.

See **Appendix 1 for Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

These gene therapies required myeloablative conditioning. Patients who were screened and enrolled followed certain procedures for discontinuation of specified medicines. Mobilization was performing with the help of certain medications, such as plerixafor, followed by apheresis to collect CD34+ stem cells for the gene therapy to be manufactured. Patients may undergo multiple rounds of apheresis to obtain an adequate number of cells for gene therapy manufacturing. If an adequate number of cells were collected, the patients underwent myeloablation with busulfan followed by the gene therapy infusion. After

treatment, patients were assessed for the study endpoints, but also hematologic markers of engraftment (e.g. platelets, absolute neutrophil count) to ensure that the bone marrow is restored and the transplanted cells grow to make all normal blood cells in addition to the cells of interest with gene alteration.

Exagamglogene autotemcel (CASGEVY, exa-cel)

Exa-cel is an autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (hHSPCs) based gene therapy approved for SCD with recurrent VOC and TDT.⁵ The studies used for publication are not fully published, though a brief initial report and protocol are available.²²

Exa-cel for Sickle Cell Disease

Evidence for efficacy and safety of exa-cel in SCD is primarily based on the CLIMB SCD -121 study, which is an on-going phase 1/2/3, single-arm, multi-center study. As data collection for this trial is ongoing, the information presented here is based on the current prescribing information⁵, clinicaltrials.gov¹, and FDA review.²⁻⁴ Most of the data reported below is from results after the June 2023 data lock. Patients aged 12 to 35 years with at least 2 severe VOC events in each of the past 2 years were included, additional inclusion/exclusion criteria are available in **Table 9**^{3,5}. As of FDA review cut-off, 63 patients had enrolled in the trial, 58 started mobilization, 44 had received exa-cel infusion (Full Analysis Set [FAS]), and 31 had the necessary minimum 16-month follow-up for analysis (Primary Efficacy Set [PES]). Those who died or discontinued due to exa-cel related AE were also included in the PES. Patients are followed 2 years post-infusion, then asked to enroll in a long-term follow-up study. Fifteen people discontinued before receiving exa-cel, 5 before mobilization, and 11 after start of mobilization. Six patients discontinued the trial due to inability to harvest sufficient cells to manufacture the product.³ Patients with SCD require plerixafor for mobilization because of contraindications for use of granulocyte-colony stimulating factor (G-CSF). One patient died after exa-cel infusion; the death was determined to be unrelated to treatment.³

The primary outcome was proportion of subjects who have not experienced any severe VOC for at least 12 consecutive months (VF12) within a 24-month evaluation window after exa-cel infusion. The median follow up duration of those in the PES was 26 months (range 17.8 to 48.1 months).^{3,5} There were no cases of graft failure or graft rejection.⁵

The evaluation of VF12 started 60 days after last RBC transfusion needed for post-transplant support or SCD disease management. The last RBC infusion was median 19 days (range 11 to 52 days) after exa-cel infusion for the PES.⁵ The VF12 occurred in 29 of 31 patients (93.5%, 98% one-sided CI 77.9 to 100.0%).⁵ There are multiple secondary endpoints are being studied including proportion of patients who were hospital free for least 12 months (HF12) starting 60 days after last RBC transfusion after exa-cel infusion, duration of time in which people were free from severe VOC, proportion of subjects with sustained fetal hemoglobin (HbF) $\geq 20\%$ over time, change in number of units of RBCs transfused for SCD over time, and HbF and hemoglobin (Hb) concentrations over time.³ Results for many of these endpoints are incomplete given the ongoing nature of study. The proportion of patients who achieved HF12 was reported as 100% for 30 PES patients who could be evaluated for this endpoint (98% one-sided CI 87.8 to 100.0%).³

The detection of persistent evidence of allelic editing in the bone marrow CD34+ cells and peripheral blood (nucleated cells) remained stable for the duration of follow-up which lasted up to month 24 in bone marrow and up to month 42 in peripheral blood.³

Exa-cel for transfusion dependent beta thalassemia

Evidence for efficacy and safety of exa-cel in TDT is primarily based on the CLIMB-THAL-111 study, which is an on-going phase 1/2/3, single-arm, open-label, multi-center study. Information presented here is extracted from the prescribing information⁵, clinicaltrials.gov⁶, and FDA review⁷. Most of the data reported below is from the results after the January 2023 data lock. Patients with TDT were eligible for enrollment (**Table 9**), and when reviewed by the FDA, 59 patients

had enrolled in the trial, begun mobilization, and were included in the safety analysis set. Fifty-two people were included in the FAS, and 35 were in the PES who had been followed for at least 16 months or continuously received RBC transfusions more than 10 months after exa-cel.⁵ Patients are followed for 2 years post-infusion, then asked to enroll in a long-term follow-up study. Mobilization was done with plerixafor and G-CSF. The primary endpoint of transfusion independence for 12 consecutive months (TI12) within a 24-month window was evaluated from 60 days after last RBC transfusion by maintaining a weighted average Hb of at least 9 g/dL. Median follow-up of the PES was 23.8 months (range 16.1 to 48.1 months).⁵ There were no cases of graft failure or graft rejection. The responder rate of TI12 was 32/35 (91.4%, 98.3% one-sided CI: 75.7%, 100%).⁵ In treatment responders (n=32), the median duration of transfusion independence was 20.8 months (range 13.3 to 45.1 months) based on the available data.⁵

The detection of persistent evidence of allelic editing in the bone marrow CD34+ cells and peripheral blood (nucleated cells) remained stable for duration of follow-up which lasted up to month 6 in bone marrow and from month 2 onward in peripheral blood.

Both study evaluations for exa-cel are limited by the ongoing nature of these clinical trials and lack of published, peer-reviewed reports. A placebo-controlled study would be unethical for a treatment that requires myeloablation, though single arm designs have inherent bias, and using a 12-month endpoint within a larger window of time, rather than a set 12-month period increases the chances of meeting the primary endpoint.³ Gene therapies are new technologies and long-term durability of response remains under investigation.

Ongoing studies of exa-cel include Climb-151, a phase 3 study of pediatric patients age 2 to 11 years with SCD and CLIMB-131, an observational study of long-term safety and efficacy of exa-cel in patients who have received the therapy in previous studies (CLIMB SCD-121, CLIMB SCD-151, CLIMB THAL-111 AND CLIMB-THAL-141).³

Lovotibeglogene autotemcel (LYFGENIA; lovo-cel)

Lovo-cel is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events. It is an insertional gene therapy using a replication-incompetent, self-inactivating lenti-virus vector (LVV).⁹

Efficacy is being established in a single-arm, open-label, multicenter, phase 1/2 study.⁹ As trials are unpublished, the information reported here is based on the prescribing information⁹, clinicaltrials.gov⁸, and FDA review⁷ with an August 2022 cut-off date for ongoing studies. Patients 12 to 35 years of age with at least 4 vaso-occlusive events (VOE) in the past 2 years were included, additional inclusion/exclusion criteria are available in **Table 9**. Forty-three patients underwent apheresis after plerixafor mobilization. Seven did not proceed to ablation, 2 withdrew due to apheresis related issues, and 5 withdrew secondary to patient or physician discretion. Thirty-six people received busulfan myeloablative treatment followed by lovo-cel infusion.⁹ The primary endpoint was complete resolution of any VOE (VOE-CR) (achieved in 28 of 32 people; 88%; 95% CI 71 to 97%) from month 6 to month 18 after lovo-cel infusion.⁹ A secondary endpoint was complete resolution of severe VOEs (sVOE-CR) (Response rate 30/32; 94%; 95% CI 79 to 99%) from month 6 to 18 months after lovo-cel infusion.⁹ VOEs were defined slightly differently than VOC as used in the exa-cel studies. VOE includes an episode of acute pain with no medically determined cause other than vaso-occlusion lasting more than 2 hours, acute chest syndrome (ACS), acute hepatic sequestration, and acute splenic sequestration. Severe VOE (sVOE) were defined as a VOE requiring a hospitalization or multiple visits to an emergency department or urgent care over 72 hours (with receipt of intravenous medications at each visit) or priapism requiring any level of medical attention.

The expression of the LVV added gene remained durable through 48 months (n=10).⁹

A phase-3 study evaluating lovo-cel in adults and children 2 years and older (HGB-210) is ongoing, and a long-term follow-up study (LTF-307) of all patients treated with lovo-cel is planned.

Similar to the exa-cel studies above, critical evaluation of the data is limited in an unpublished trial. In clinical studies of lovo-cel, a fixed 12-month timeframe was used to evaluate endpoints compared to studies of exa-cel, which may lower risk of detection bias (**Table 9**). Inclusion criteria in studies evaluating lovo-cel permitted patients to enroll with a lower score on the Karnofsky and Lansky performance status, allowing patients who may have a lower functional status to participate compared to studies evaluating exa-cel. The different mechanisms lead to some difference in patient selection, and LVV such as lovo-cel cannot be given to patients with certain viral illnesses, in addition to the risk of infection that comes from myeloablative conditioning. Gene therapies are new technologies and long-term durability of response remains under investigation.

Clinical Safety:

Exa-cel: Sickle Cell Disease

The mean duration of follow-up for the FAS was 19.3 months (range 0.8 to 48.1 months).⁵ Serious AE after myeloablative conditioning occurred in 45% of patients and one patient died secondary to a COVID-19 infection and respiratory failure. The most common serious adverse reactions (≥ 2 patients) were cholelithiasis, pneumonia, abdominal pain, constipation, pyrexia, upper abdominal pain, non-cardiac chest pain, oropharyngeal pain, pain, and sepsis.⁵ Grade 3 or 4 adverse reactions occurring in at least 10% of patients are in **Table 1 and Table 2**.

Table 1. Non-laboratory grade 3 or 4 adverse events in at least 10% of patients receiving exa-cel for SCD⁵

Adverse Event	Patients (N=44) N (%)
Mucositis	38 (86)
Febrile neutropenia	21 (48)
Decreased appetite	18 (41)
Musculoskeletal pain	6 (14)
Abdominal pain	5 (11)
Cholelithiasis	5 (11)
Pruritus	5 (11)

Table 2. Laboratory grade 3 or 4 adverse events in at least 10% of patients receiving exa-cel for SCD⁵

Adverse Event	Patients (N=44) (%)
Neutropenia	100
Thrombocytopenia	100
Leukopenia	98
Anemia	84
Lymphopenia	50
CD4 lymphocytes decreased	23

Activated partial thromboplastin time prolonged	16
Hyperbilirubinemia	14

Platelet engraftment after myeloablative treatment was defined as 3 consecutive measurements of platelet counts $\geq 50 \times 10^9/L$, obtained on 3 different days, without administration of platelet transfusions for 7 days. The median time to platelet engraftment was 35 days (range 23 to 126 days).⁵ This is a delay in engraftment compared to other published outcomes of SCD patients receiving allogeneic hematopoietic stem cell transplant,³ though there was no association observed between bleeding events and time to platelet engraftment.⁵

Neutrophil engraftment after myeloablative treatment was defined as 3 consecutive measurements of absolute neutrophil count (ANC) ≥ 500 cells/ μ L on 3 different days, without use of the unmodified rescue CD34+ cells. The median time to neutrophil engraftment was 27 days (range 15 to 40 days).⁵ There was no association observed between infections and time to neutrophil engraftment or use of rescue CD34+ cells.⁵

Exa-cel: Beta thalassemia

The mean duration of follow-up for the FAS was 20.4 months (range 2.1 to 48.1 months). Serious AE after myeloablative conditioning occurred in 33% of patients. The most common serious adverse reactions (≥ 2 patients) were veno-occlusive liver disease, pneumonia, hypoxia, thrombocytopenia, viral infection, and upper respiratory tract infection. Grade 3 or 4 adverse reactions occurring in at least 10% of patients are in **Table 3 and Table 4**.⁵

Table 3. Non-laboratory grade 3 or 4 adverse events in at least 10% of patients receiving exa-cel for TDT⁵

Adverse Event	Patients (N=52) N (%)
Mucositis	37 (71)
Febrile neutropenia	28 (54)
Decreased appetite	12 (23)
Epistaxis	7 (13)
Veno-occlusive liver disease	5 (10)

Table 4. Laboratory grade 3 or 4 adverse events in at least 10% of patients receiving exa-cel for TDT⁵

Adverse Event	Patients (N=52) (%)
Neutropenia	100
Thrombocytopenia	100
Leukopenia	98
Anemia	92
Lymphopenia	79
CD4 lymphocytes decreased	23
Hyperbilirubinemia	23
Alanine aminotransferase increased	19

Hypokalemia	19
Gamma-glutamyltransferase increased	17
Activated partial thromboplastin time prolonged	13
Hypocalcemia	12

Platelet engraftment was defined as 3 consecutive measurements of platelet counts $\geq 20 \times 10^9/L$, obtained on 3 different days, without administration of platelet transfusions for 7 days. The median time to platelet engraftment was 44 days (range 20 to 200 days).⁵ Patients without a spleen had an earlier mean time to engraftment. There is increased risk of bleeding until engraftment, but no association was observed between bleeding events and time to platelet engraftment.

Neutrophil engraftment was defined as 3 consecutive measurements of ANC ≥ 500 cells/ μL on 3 different days, without use of the unmodified rescue CD34+ cells. The median time to neutrophil engraftment was 29 days (range 12 to 56 days).⁵ There was no association observed between infections and time to neutrophil engraftment and no patients received rescue CD34+ cells.

Off target gene editing was not seen in healthy donors or patients, though the risk cannot be ruled out due to genetic variants. The effect of exa-cel on fertility is unknown, but patients should be aware of risk for infertility due to myeloablative protocol and options for fertility preservation.⁵

Lovo-cel: Sickle Cell Disease

FDA labeling for lovo-cel indication includes limitations for use in people with α -thalassemia trait ($-\alpha 3.7/-\alpha 3.7$) who may experience anemia with erythroid dysplasia requiring chronic red blood cell transfusions.⁹ Lovo-cel has not been studied in patients with more than two α -globin gene deletions. It also has a box warning for risk of malignancy. Two patients in an earlier study (using a different manufacturing process and transplant procedure) developed AML and one patient with α -thalassemia trait was diagnosed with MDS.⁹ Recipients of lovo-cel should have complete blood counts at least every 6 months and through integration site analysis at months 6, 12, and every 6 months for at least 15 years.⁹ Patients may falsely test positive for HIV after lovo-cel treatment.⁹

No patients experienced graft failure or rejection. Most patients (73%) experienced at least one serious adverse reaction; most were related to myeloablative conditioning or the underlying disease.⁹

Platelet engraftment was defined as 3 consecutive measurements of platelet counts $\geq 50 \times 10^9/L$, obtained on 3 different days, without administration of platelet transfusions for 7 days. The median time to platelet engraftment was 37 days (range 19 to 235 days)⁹, similar to the delayed engraftment seen with exa-cel in patients with SCD.

Neutrophil engraftment was defined as 3 consecutive measurements of ANC ≥ 500 cells/ μL on 3 different days, without use of the unmodified rescue CD34+ cells. The median time to neutrophil engraftment was 20 days (range 12 to 35 days).⁹ There was no association observed between infections and time to neutrophil engraftment and no patients received rescue CD34+ cells.

The effect of lovo-cel on fertility is unknown, but patients should be aware of risk for infertility due to myeloablative protocol and options for fertility preservation.⁹

Table 6. Grade 3 or 4 adverse events in at least 10% of patients receiving lovo-cel for SCD⁹

Adverse Event	Patients (N=45) (%)
Stomatitis	71
Thrombocytopenia	69
Neutropenia	60
Febrile neutropenia	44
Anemia	33
Leukopenia	33
Aspartate aminotransferase increased	18
Sickle cell anemia with crisis	16
Alanine aminotransferase increased	13
Gamma-glutamyltransferase increased	13
Decreased appetite	11
Pharyngeal inflammation	11

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Freedom from VOC/VOE (SCD) or RBC transfusions (TDT)
- 2) Quality of life
- 3) Reduced hospitalizations
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Proportion VF12 (Exa-cel SCD)
- 2) Proportion TI12 (Exa-cel TDT)
- 3) Complete resolution of VOE and severe VOE (Lovo-cel SCD)

Table 7. Exagamglogene autotemcel (CASGEVY) Pharmacology and Pharmacokinetic Properties⁵

Parameter	
Mechanism of Action	Cellular gene therapy of autologous CD34 ⁺ HCSs edited by CRISPR/Cas9-technology at the erythroid specific enhancer region of the BCL11A gene to reduce BCL11A expression in erythroid lineage cells, leading to increased fetal hemoglobin (HbF) protein production Edited CD34 ⁺ cells engraft in the bone marrow and differentiate to erythroid lineage cells with reduced BCL11A expression. Reduced BCL11A expression results in an increase in γ -globin expression and HbF protein production in erythroid cells. In patients with severe sickle cell disease, HbF expression reduces intracellular hemoglobin S (HbS) concentration, preventing the red blood cells from sickling and addressing the underlying cause of disease, thereby eliminating VOCs. In patients with transfusion-dependent β -thalassemia, γ -globin production improves the α -globin to non- α -globin imbalance
Oral Bioavailability	Not applicable (N/A)

Distribution and Protein Binding	N/A
Elimination	N/A
Half-Life	N/A
Metabolism	N/A

Table 8. Lovotibeglogene autotemcel (LYFGENIA) Pharmacology and Pharmacokinetic Properties.⁹

Parameter	
Mechanism of Action	Gene therapy adds functional copies of a modified β A-globin gene (threonine [T] replaced with glutamine [Q] at position 87, T87Q or β A-T87Q-globin) into patients' hematopoietic stem cells (HSCs) through transduction of autologous CD34+ cells with BB305 lenti-virus vector (LVV). The transduced CD34+ HSCs engraft in the bone marrow and differentiate to produce red blood cells containing biologically active β A-T87Q-globin that will combine with α -globin to produce functional hemoglobin (Hb) containing β A-T87Q-globin (HbAT87Q).
Oral Bioavailability	Not applicable (N/A)
Distribution and Protein Binding	N/A
Elimination	N/A
Half-Life	N/A
Metabolism	N/A

Table 9. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. CLIMB SCD-121 ¹⁻⁵ NCT03745287 SA, MC, OL ongoing, phase 1/2/3	1. Exagamglogene autotemcel Eligible patients underwent mobilization and apheresis to collect CD34+ stem cells for gene therapy manufacture, followed by myeloablative conditioning and infusion of exagamglogene	Demographics: <i>By June 2023 data lock</i> - 18 to 35 y: 73-77% - 12 to <18 y: 23-27% - median age ~21, range 12 to 34 y - Female 45% - Black 86-87% - White 3-7% - β^S/β^S genotype: 91-97% - β^S/β^0 genotype: 3-7% - Annualized severe VOCs: 3.5/y (range 2.0 to 18.5) - Annualized hospitalizations: 2.0-2.5/y (range 0.5 to 8.5)	By time of FDA analysis FAS (safety): 44 PES (efficacy): 31*	Primary Endpoint: Proportion VF12 Response rate 29/31 (93.5%) (98% one-sided CI 77.9 to 100.0%) Secondary Endpoints: Proportion HF12 Response rate 30/30 (100%) (one patient not	N/A	SAE: 45% (most common: cholelithiasis, pneumonia, abdominal pain, constipation, pyrexia, upper abdominal pain, non-cardiac chest pain, oropharyngeal pain, pain, and sepsis)	N/A	Risk of Bias (low/high/unclear): <u>Selection Bias</u> (High) Single-arm design <u>Performance Bias</u> : (Unclear) Single-arm, OL study with a subjective (pain) endpoint <u>Detection Bias</u> : (High) Time to event metric with subjective (pain) endpoint. Reported VOC were adjudicated by an independent committee (EAC), but pain adverse events were evaluated by investigators then submitted to EAC which could further pain AE submission and increase risk of bias. FDA statistician calculated that use of a flexible time range instead of fixed 12-month period increased likelihood of study success by 2 to 3-fold.

	<p>autotemcel cell suspension $\geq 3.0 \times 10^6$ CD34+ cells/kg single cells dose for infusion.</p> <p>Dose median 4.0 (range 2.9 to 14.4) $\times 10^6$ CD34+ cells/kg</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> -12 to 35 years -β^S/β^S, β^S/β^0, or β^S/β^+ genotype -hx of at least 2 severe VOC events in each of 2 y before screening <ul style="list-style-type: none"> ·Acute pain event ·Acute chest syndrome ·Priapism ·Splenic sequestration -normal TCD in middle cerebral and internal carotid artery for subjects 12 to 16 y -Karnofsky performance status $\geq 80\%$ if ≥ 16 y or Lansky performance status of $\geq 80\%$ if < 16y <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> - advanced liver disease -baseline GFR < 60 ml/min/1.73 m² -HbF $> 15.0\%$ -history of untreated Moyamoya disease or condition that increases bleeding risk -hx of abnormal TCD in middle cerebral and internal carotid artery -willing & healthy 10/10 HLA matched related hematopoietic stem cell donor or prior allogeneic HSCT - >10 unplanned hospitalizations or ED visits related to chronic pain rather than SCD acute pain crises in year before screening -WBC $< 3 \times 10^9/L$ -PLT $< 50 \times 10^9/L$ (not related to hypersplenism) -LVEF $< 45\%$ -DLCO $< 50\%$ 		<p>evaluable for endpoint) (98% one-sided CI: 87.8 to 100.0%)</p>				<p>Attrition Bias: (Unclear) Ongoing study, unable to assess risk of bias Reporting Bias: (Unclear) Unpublished, ongoing study, unable to assess risk of bias Other Bias: (Unclear) Trial funded by manufacturer.</p> <p>Applicability: Patient: Representative of population with SCD. Most applicable to people with β^S/β^S genotype. Patients with end organ damage or low functional performance were generally excluded. Intervention: CRISPR/Cas9 based gene editing therapy Comparator: None, placebo control would be unethical in a drug requiring myeloablation. Outcomes: VOC events and hospitalizations appropriate for condition, some concerns related to time definition. Duration of response and full trial results are pending. Setting: 16 sites in US, Canada, United Kingdom, France, Belgium, Germany, and Italy. Bulk of data from single US center.</p>
<p>2. CLIMB-THAL-111²⁻⁶ NCT 03655678</p> <p>SA, OL, MC, ongoing, phase 1/2/3</p>	<p>1. Exagamglogene autotemcel</p> <p>Eligible patients underwent mobilization and apheresis to collect CD34+ stem cells for gene therapy manufacture,</p>	<p>Demographics: <i>By Jan 2023 data lock</i> Age</p> <ul style="list-style-type: none"> - 18 to 25 y: 65.4-68.6% -12 to <18 y: 31.4-34.6% -median age 20, range 12 to 35 y <p>Female ~48%</p> <p>Race</p> <ul style="list-style-type: none"> - Asian 37.1-42.3% - White 34.6-42.9% 	<p>FAS: 52</p> <p>PES: 35</p>	<p>Primary Endpoint: Proportion T112</p> <p>Response rate 32/35 (91.4%) (98.3% one-sided CI: 75.7%, 100%)</p>	N/A	<p>SAE: 33% (most common: veno-occlusive liver disease, pneumonia, hypoxia, thrombocytopenia, viral infection, and</p>	N/A	<p>Risk of Bias (low/high/unclear): Approval was based on an interim analysis of a secondary endpoint. Interim results are unpublished and the study is ongoing. Risk of bias cannot be fully assessed.</p> <p>Selection Bias Performance Bias Detection Bias: (high) Time to event metric. Flexible time range instead of fixed 12-month</p>

	<p>followed by myeloablative conditioning and infusion of exagamglogene autotemcel cell suspension $\geq 3.0 \times 10^6$ CD34+ cells/kg single cells dose for infusion.</p> <p>Dose median 7.5 (range 3.0 to 19.7) x 10^6 CD34+ cells/kg</p>	<p>Genotype</p> <ul style="list-style-type: none"> -β^0/β^0 -like genotype: 57.1-59.6% - non-β^0/β^0 -like genotype: 40.4-42.9% - Annualized median RBC t/f volume: 201-205 mL/kg (range 48-331) - Annualized median RBC t/f episodes: 17 (range 5-35) - spleen intact 26-36% <p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> - 12-35 y old -documented homozygous β-thalassemia or compound heterozygous β-thalassemia including β-thalassemia /HbE - hx ≥ 100 mL/kg/y or 10 unit/y packed RBC t/f for 2 years <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> - severely elevated iron in heart (cardiac T2* less than 10 msec by MRI or LVEF < 45% - advanced liver disease - willing & healthy 10/10 HLA matched related hematopoietic stem cell donor or prior allogeneic HSCT - Sickle cell beta thalassemia variant - clinically significant, active infection - WBC < 3×10^9/L -PLT < 50×10^9/L (not related to hypersplenism) - associated α-thalassemia or >1 α deletion or α multiplications. 				upper respiratory tract infection)	<p>period increased likelihood of study success.</p> <p>Attrition Bias:</p> <p>Reporting Bias: (Unclear) Trial funded by manufacturer.</p> <p>Other Bias:</p> <p>Applicability:</p> <p>Patient: Demographics generally representative of TDT population. Enrolled patients generally had received double the transfusion volume or number of transfusions needed for inclusion criteria.</p> <p>Intervention: CRISPR/Cas9 based gene editing therapy</p> <p>Comparator: None, placebo control would be unethical in drug requiring myeloablation.</p> <p>Outcomes: Transfusions are an important clinical outcome for transfusion dependent thalassemia Duration of response and full trial results pending.</p> <p>Setting: 13 sites in US, Canada, United Kingdom, Germany, and Italy.</p>	
<p>3. HB 206⁷⁻⁹ NCT02140554</p> <p>SA, OL, MC, phase 1/2</p>	<p>1. Lovotibeglogene autotemcel</p> <p>Eligible patients underwent mobilization and apheresis to collect CD34+ stem cells for gene therapy manufacture, followed by</p>	<p>Demographics:</p> <p>Age</p> <ul style="list-style-type: none"> - ≥ 18 y: 75-78% - 12 to <18 y: 22-25% - median age 24-25, range 12 to 38 y <p>Female 37-39%</p> <p>Black 97%</p> <p>Current smoker: 3-14%</p> <p>Genotype</p> <ul style="list-style-type: none"> -β^S/β^S genotype: 100% - α-globin genotype 	<p>By time of FDA analysis</p> <p>FAS (safety): 36</p> <p>PES (efficacy): 32</p>	<p>Primary Endpoint: VOE-CR between month 6 and 18</p> <p>Response rate 28/32 (88%) (95% CI 71 to 97%)</p> <p>Secondary Endpoints:</p>	N/A	<p>SAE: 73%</p> <p>No recurrent stroke in 5 patients enrolled with history (44-60 months follow-up)</p> <p>Deaths:</p>	N/A	<p>Risk of Bias (low/high/unclear): Approval was based on an interim analysis of a secondary endpoint. Interim results are unpublished. Risk of bias cannot be fully assessed.</p> <p>Selection Bias</p> <p>Performance Bias</p> <p>Detection Bias</p> <p>Attrition Bias</p> <p>Reporting Bias</p>

<p>myeloablative conditioning and infusion of lovotibeglogene autotemcel cell suspension $\geq 3.0 \times 10^6$ CD34+ cells/kg single cells dose for infusion.</p> <p>Dose median 6.4 (range 3 to 14) $\times 10^6$ CD34+ cells/kg</p>	<p>$\cdot\alpha\alpha/\alpha\alpha$: 63-64% $\cdot\alpha\alpha/-\alpha 3.7$: 31% $\cdot-\alpha 3.7/-\alpha 3.7$: 6%</p> <p>Hx stroke/vasculopathy: 5 (14%)</p> <p>Key Inclusion Criteria: - ≥ 12 to ≤ 50 y - β^s/β^s, β^s/β^0, or β^s/β^+ genotype -hx of at least 4 severe VOE in 2 y before screening</p> <ul style="list-style-type: none"> -Acute pain event -Acute chest syndrome -Acute hepatic sequestration -Acute splenic sequestration -priapism requiring medical attention -hydroxyurea failure or intolerance -Karnofsky performance status $\geq 60\%$ if ≥ 16 y or Lansky performance status of $\geq 60\%$ if < 16y -followed and treated for SCD for past 24 months with medical records <p>Key Exclusion Criteria: - HIV, HBV, HCV positive - clinically significant, active infection - Any history of severe cerebral vasculopathy (radiologic evidence of silent infarction allowed) -ANC < 1000/microL or < 500 on while on hydroxyurea -PLT $< 100,000$/microL -advanced liver disease</p>		<p>sVOE-CR between month 6 and 18</p> <p>Response rate 30/32 (94%) (95% CI 79 to 99%)</p>	<p>3 (cumulative from all lova-cel trials)</p> <ul style="list-style-type: none"> - 1: sudden cardiac death due to underlying disease - 2: AML 	<p>Other Bias</p> <p>Applicability: <u>Patient:</u> Representative of disease population. Patients with end organ damage were generally excluded. Inclusion criteria may allow patients with lower performance status than exa-cel therapy inclusion. <u>Intervention:</u> LVV based insertional gene therapy. Dose based on earlier studies. <u>Comparator:</u> None, placebo control would be unethical for a drug requiring myeloablation. <u>Outcomes:</u> VOE events appropriate for condition. Duration of response and full trial results are pending. <u>Setting:</u> 11 sites in US</p>
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Abbreviations: AE = Adverse events; AML = acute myeloid leukemia; ANC = absolute neutrophil count; ARR = absolute risk reduction; CI = confidence interval; DLCO = diffusing capacity of the lungs for carbon monoxide; EAC = endpoint adjudication committee; ED = emergency department; FAS = full analysis set; FDA = Food and Drug Administration; HbE = hemoglobin E; HbF = fetal hemoglobin; HBV = hepatitis B virus; HCV = hepatitis C virus; HF12 = Hospitalization free for 12 consecutive months; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplant; hx = history; LVEF = left ventricular ejection fraction; mITT = modified intention to treat; MRI = magnetic resonance imaging; N = number of subjects; N/A = not applicable; NNH = number needed to harm; NNT = number needed to treat; OL = open-label; PES = primary efficacy set; PLT = platelet; RBC = red blood cell; SA = single-arm; SAE = serious adverse event; sVOE-CR = complete resolution of severe VOE; sVOC = recurrent severe VOC; TCD = transcranial doppler; t/f = transfusion; T12 = transfusion-independence for 12 consecutive months; US = United States; VF12 = VOC free for 12 consecutive months; VOC = vaso-occlusive crisis; vaso-occlusive event; VOE-CR = complete resolution of VOE; WBC = white blood cell; y = year.

* PES reported as 30 in FDA clinical review and 31 in prescribing information due to redefinition to include an additional patient who had less than 16 months follow up but determined to be a non-responder for the primary efficacy endpoint.

References:

1. A Safety and Efficacy Study Evaluating CTX001 in Subjects With Severe Sickle Cell Disease. NCT03745287. Food and Drug Administration. Accessed April 8, 2024. Available at: <https://clinicaltrials.gov/study/NCT03745287?term=NCT03745287&rank=1>.
2. Clinical Pharmacology BLA Review. BLA 125785/0. Food and Drug Administration. Accessed April 5, 2024. Available at: <https://www.fda.gov/vaccines-blood-biologics/casgevy>.
3. BLA Clinical Review Memorandum. STN 125787/0. Food and Drug Administration. Accessed April 4, 2024. Available at: <https://www.fda.gov/vaccines-blood-biologics/casgevy>.
4. Clinical Pharmacology BLA Review: Submission number 125787.00. Food and Drug Administration. Accessed April 5, 2024. Available at: <https://www.fda.gov/vaccines-blood-biologics/casgevy>
5. Casgevy (exagamglogene autotemcel) Prescribing Information. Vertex Pharmaceuticals. Boston, MA. January 2024. Available at: <https://www.fda.gov/media/175481/download?attachment>
6. A Safety and Efficacy Study Evaluating CTX001 in Subjects With Transfusion-Dependent β -Thalassemia. NCT03655678. Available at: <https://clinicaltrials.gov/study/NCT03655678?term=NCT03655678&rank=1#study-overview> Accessed: April 9, 2024.
7. Clinical Pharmacology BLA Review. BLA 125788/0. Food and Drug Administration. Accessed April 4, 2024. Available at: <https://www.fda.gov/vaccines-blood-biologics/lyfgenia>.
8. A Study Evaluating the Safety and Efficacy of bb1111 in Severe Sickle Cell Disease. NCT02140554. Available at: <https://clinicaltrials.gov/study/NCT02140554?intr=BB1111&rank=1#study-plan> Accessed April 9, 2024.
9. Lyfgenia (lovotibeglogene autotemcel) Prescribing Information. bluebird bio. Somerville, MA. December 2023. Available at: <www.fda.gov/media/174610/download?attachment>.
10. Pharmacists Letter. Management of Sickle Cell Disease. December 2017. Available at: <https://pharmacist.therapeuticresearch.com/Content/Segments/PRL/2015/Feb/Management-of-Sickle-Cell-Disease-8101>. Accessed February 14, 2020. .
11. Food and Drug Administration. Multi-disciplinary report: Voxelotor. Centers for Drug Evaluation and Research. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213137Orig1s000Multidiscipline.pdf. Accessed February 9, 2020. .
12. Cooper T, Hambleton I, Ballas S. Pharmacological Interventions for Painful Sickle Cell Vaso-occlusive crises in adults. Cochrane Systematic Review. November 19, 2019. .
13. Nevitt S, Jones A, Howard J. Hydroxyurea (hydroxycarbamide) for sickle cell disease. Cochrane Database of Systematic Reviews. 2017. Issue 4. Art. No.: CD002202. Accessed January 21, 2020. .
14. Food and Drug Administration. Mult-Discipline Review - Crizanlizumab. Centers for Drug Evaluation and Research. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761128Orig1s000MultidisciplineR.pdf. Accessed February 17, 2020. .
15. Yawn B, Buchanan G, Afenyi-Annan A, Ballas S. Management of Sickle Cell Disease: Summary of the 2014 Evidence-Based Report by Expert Panel Members | Guidelines | JAMA | JAMA Network. <https://jamanetwork-com.liboff.ohsu.edu/journals/jama/fullarticle/1902235>. Accessed February 19, 2020. .
16. Overview of variant sickle cell syndromes – UpToDate. https://www.uptodate-com.liboff.ohsu.edu/contents/overview-of-variant-sickle-cell-syndromes?search=sick%20cell%20disease%20pathophysiology&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H9. Accessed March 17, 2020. .

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17. Kim KH, Oh KY. Clinical applications of therapeutic phlebotomy. *J Blood Med*. 2016;7:139-144. doi:10.2147/JBM.S108479.
 18. Lindsey WT, Steuber TD, Grabowsky AB. Gene therapies for sickle cell disease and transfusion-dependent beta thalassemia. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2022.
 19. DynaMed. Beta-Thalassemia Major and Intermedia. EBSCO Information Services. Accessed July 3, 2023. <https://www.dynamed.com/condition/beta-thalassemia-major-and-intermedia#GUID-CA33D0DD-80A1-49D3-B041-C7396B30A546>.
 20. Thompson AA, Walters MC, Kwiatkowski J, et al. Gene Therapy in Patients with Transfusion-Dependent β -Thalassemia. *New England Journal of Medicine*. 2018;378(16):1479-1493.
 21. Zynteglo (betibeglogene autotemcel) package insert. bluebird bio, Inc. Somerville, MA: <https://www.fda.gov/media/160991/download>. August 2022.
 22. *N Engl J Med*. 2021; 384:252-260 DOI: 10.1056/NEJMoa2031054

DRAFT

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CASGEVY™ safely and effectively. See full prescribing information for CASGEVY

CASGEVY (exagamglogene autotemcel), suspension for intravenous infusion

Initial U.S. Approval: 2023

RECENT MAJOR CHANGES

Indications and Usage, Transfusion-dependent β-thalassemia (1)	01/2024
Dosage and Administration (2.2)	01/2024
Warnings and Precautions, Neutrophil Engraftment Failure (5.1)	01/2024
Warnings and Precautions, Delayed Platelet Engraftment (5.2)	01/2024

INDICATIONS AND USAGE

CASGEVY is an autologous genome edited hematopoietic stem cell-based gene therapy indicated for the treatment of patients aged 12 years and older with:

- sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs). (1)
- transfusion-dependent β-thalassemia (TDT). (1)

DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

- Patients are required to undergo hematopoietic stem cell (HSC) mobilization followed by apheresis to obtain CD34⁺ cells for CASGEVY manufacturing. (2.2)
- Dosing of CASGEVY is based on body weight. The minimum recommended dose is 3×10^6 CD34⁺ cells/kg. (2.1, 2.3)
- Full myeloablative conditioning must be administered between 48 hours and 7 days before infusion of CASGEVY. (2.2)
- Prophylaxis for seizures should be considered prior to initiating myeloablative conditioning. (2.2)
- Verify that the patient's identity matches the unique patient identification information on the product labels and Lot Information Sheet prior to thaw and infusion. (2.2)
- Do not sample, alter, or irradiate CASGEVY. (2.2)
- Do not use an in-line blood filter when infusing CASGEVY. (2.3)
- Administer each vial of CASGEVY via intravenous infusion within 20 minutes of thaw. (2.3)

DOSAGE FORMS AND STRENGTHS

- CASGEVY is a cell suspension for intravenous infusion. (3)
- The minimum recommended dose of CASGEVY is 3×10^6 CD34⁺ cells per kg of body weight, which may be composed of multiple vials. (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- **Neutrophil Engraftment Failure:** Monitor absolute neutrophil counts (ANC) after CASGEVY infusion. Administer rescue cells in the event of neutrophil engraftment failure. (5.1)
- **Delayed Platelet Engraftment:** Monitor platelet counts until platelet engraftment and recovery are achieved. Patients should be monitored for bleeding. (5.2)
- **Hypersensitivity Reactions:** Monitor for hypersensitivity reactions during and after infusion. (5.3)
- **Off-Target Genome Editing Risk:** Although not observed in healthy donors and patients, the risk of unintended, off-target editing in CD34⁺ cells due to genetic variants cannot be ruled out. (5.4)

ADVERSE REACTIONS

The most common Grade 3 or 4 non-laboratory adverse reactions (incidence $\geq 25\%$) were mucositis and febrile neutropenia in patients with SCD and TDT, and decreased appetite in patients with SCD. (6)

The most common Grade 3 or 4 laboratory abnormalities ($\geq 50\%$) were neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Vertex Pharmaceuticals Incorporated at 1-877-634-8789 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Granulocyte-Colony Stimulating Factor:** Granulocyte-Colony Stimulating Factor (G-CSF) must not be used for CD34⁺ HSC mobilization of patients with SCD. (7.1)
- **Hydroxyurea:** Discontinue hydroxyurea at least 8 weeks prior to start of mobilization and conditioning. (7.2)
- **Voxelotor and Crizanlizumab:** Discontinue the use of voxelotor and crizanlizumab at least 8 weeks prior to start of mobilization and conditioning. (7.3)
- **Iron Chelators:** Discontinue iron chelators at least 7 days prior to initiation of myeloablative conditioning. 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. (7.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 01/2024

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LYFGENIA safely and effectively. See full prescribing information for LYFGENIA.

LYFGENIA® (lovotibeglogene autotemcel) suspension for intravenous infusion

Initial U.S. Approval: 2023

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)

INDICATIONS AND USAGE

LYFGENIA is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events. (1)

Limitations of Use

Following treatment with LYFGENIA, patients with α -thalassemia trait ($-\alpha 3.7/-\alpha 3.7$) may experience anemia with erythroid dysplasia that may require chronic red blood cell transfusions. LYFGENIA has not been studied in patients with more than two α -globin gene deletions. (1)

DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

- Patients are required to undergo hematopoietic stem cell (HSC) mobilization followed by apheresis to obtain CD34+ cells for LYFGENIA manufacturing. (2.2)
- Dosing of LYFGENIA is based on the number of CD34+ cells in the infusion bag(s) per kg of body weight. (2.1)
- The minimum recommended dose is 3×10^6 CD34+ cells/kg. (2.1)
- Myeloablative conditioning must be administered before infusion of LYFGENIA. (2.2)
- Following myeloablative conditioning, allow a minimum of 48 hours of washout before LYFGENIA infusion. (2.2)
- Verify that the patient's identity matches the unique patient identification information on the LYFGENIA infusion bag(s) prior to infusion. (2.2)
- Do not sample, alter, irradiate, or refreeze LYFGENIA. (2.2)
- Do not use an in-line blood filter or an infusion pump. (2.3)
- Administer LYFGENIA within 4 hours after thawing. (2.3)

- Administer each infusion bag of LYFGENIA via intravenous infusion over a period of less than 30 minutes. (2.3)

DOSAGE FORMS AND STRENGTHS

LYFGENIA is a cell suspension for intravenous infusion. (3)

A single dose of LYFGENIA contains a minimum of 3×10^6 CD34+ cells/kg of body weight, in one to four infusion bags. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- **Delayed Platelet Engraftment:** Monitor patients frequently for thrombocytopenia and bleeding until platelet engraftment and platelet recovery are achieved. (5.2)
- **Neutrophil Engraftment Failure:** Monitor absolute neutrophil counts (ANC) after LYFGENIA infusion. If neutrophil engraftment does not occur, administer rescue cells. (5.3)
- **Insertional Oncogenesis:** There is a potential risk of insertional oncogenesis after treatment with LYFGENIA. (5.4)
- **Hypersensitivity Reactions:** Monitor for hypersensitivity reactions during infusion. (5.5)

ADVERSE REACTIONS

Most common adverse reactions \geq Grade 3 (incidence \geq 20%) were stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact bluebird bio at 1-833-999-6378 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Anti-retrovirals:** Discontinue anti-retroviral medications at least one month prior to mobilization and until all cycles of apheresis are completed. There are some long-acting anti-retroviral medications that may require a longer duration of discontinuation for elimination of the medication. (7.2)
- **Hydroxyurea:** Discontinue 2 months prior to mobilization and 2 days prior to conditioning. (7.3)
- **Iron chelation:** Discontinue at least 7 days prior to mobilization and conditioning. (7.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2023

Exagamglogene Autotemcel

Goal(s):

- Approve Exagamglogene autotemcel (CASGEVY) for conditions supported by evidence of benefit

Length of Authorization:

- Once in a lifetime dose.

Requires PA:

- Exagamglogene autotemcel (billed as pharmacy or physician administered claim)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Is there documentation that the patient has never received another gene therapy or hematopoietic stem cell transplant for any diagnosis?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is the medication being ordered by, or in consultation with, a hematologist?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness
5. Does patient have confirmed beta thalassemia?	Yes: Go to #6	No: Go to #7

Approval Criteria		
<p>6. Is the patient transfusion dependent, defined as requiring in each of the past 2 years:</p> <ul style="list-style-type: none"> • 100 mL/kg/year or more of packed red blood cells (any patient age) OR • 8 transfusions or more of packed red blood cells per year 	Yes: Go to #8	No: Pass to RPh. Deny; medical appropriateness
<p>7. Does the patient have Sickle Cell Disease with recurrent vaso-occlusive crisis (VOC)?</p> <p>Note: Recurrent VOC defined as at least 2 VOC events/year for more than one year. Examples of VOC include acute chest syndrome, priapism lasting > 2 hours and requiring visit to medical facility, acute pain event requiring visit to medical facility and pain medications (e.g. opioids, injectable non-steroidal anti-inflammatory drugs) or red blood transfusion, acute splenic sequestration, or acute hepatic sequestration.</p>	Yes: Go to #8	No: Pass to RPh. Deny; medical appropriateness
8. Is the patient 12 years old or older?	Yes: Go to #9	No: Pass to RPh. Deny; medical appropriateness
9. Does the patient have cirrhosis or advanced liver disease?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #10
10. Is there documentation that the patient does not have active or chronic infections of HIV, hepatitis B, or hepatitis C?	Yes: Go to #11	No: Pass to RPh. Deny; medical appropriateness
11. Does the prescriber attest that the patient's general health and comorbidities have been assessed and that the patient is expected to safely tolerate myeloablation?	Yes: Go to #12	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
12. Is the patient of childbearing potential OR capable of fathering a child?	Yes: Go to #13	No: Go to #15
13. Is the patient pregnant, actively trying to conceive, or trying to father a child?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Go to #14
14. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant or father a child during treatment and for at least 6 months after administration of the gene therapy?	Yes: Go to #15	No: Pass to RPh. Deny; medical appropriateness
15. Is there documentation that the provider and patient have discussed risks of myeloablative treatment on future fertility and options for fertility-preservation?	Yes: Approve for one lifetime dose	No: Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 6/24 (SF)
 Implementation: TBD

Lovotibeglogene Autotemcel

Goal(s):

- Approve lovotibeglogene autotemcel (LYFGENIA) for conditions supported by evidence of benefit

Length of Authorization:

- Once in a lifetime dose.

Requires PA:

- Lovotibeglogene autotemcel (LYFGENIA) (billed as pharmacy or physician administered claim)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Is there documentation that the patient has never received another gene therapy or hematopoietic stem cell transplant for any diagnosis?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is the medication being ordered by, or in consultation with, a hematologist?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness
5. Does the patient have Sickle Cell Disease with recurrent vaso-occlusive crisis (VOC)? Note: Recurrent VOC defined as at least 2 VOC events/year for more than one year. Examples of VOC include acute chest syndrome, priapism lasting > 2 hours and requiring visit to medical facility, acute pain event requiring visit to medical facility and pain medications (e.g. opioids, injectable non-steroidal anti-inflammatory drugs) or red blood transfusion, acute splenic sequestration, or acute hepatic sequestration.	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness
6. Is the patient 12 years old or older?	Yes: Go to #7	No: Pass to RPh. Deny; medical appropriateness
7. Does the patient have cirrhosis or advanced liver disease?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #8
8. Does the patient have α -thalassemia trait ($-\alpha^{3.7}/-\alpha^{3.7}$) or more than two α -globin gene deletions?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #9

Approval Criteria		
9. Is there documentation that the patient does not have active or chronic infections of HIV, hepatitis B, or hepatitis C?	Yes: Go to #10	No: Pass to RPh. Deny; medical appropriateness
10. Does the prescriber attest that the patient's general health and comorbidities have been assessed and that the patient is expected to safely tolerate myeloablation?	Yes: Go to #11	No: Pass to RPh. Deny; medical appropriateness
11. Has the patient (and/or guardian, if applicable) been educated on the risk of insertional oncogenesis and need for lifelong monitoring (bloodwork) at every 6 months?	Yes: Go to #12	No: Pass to RPh. Deny; medical appropriateness
12. Is the patient of childbearing potential OR capable of fathering a child?	Yes: Go to #13	No: Go to #15
13. Is the patient pregnant, actively trying to conceive, or trying to father a child?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Go to #14
14. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant or father a child during treatment and for at least 6 months after administration of the gene therapy?	Yes: Go to #15	No: Pass to RPh. Deny; medical appropriateness
15. Is there documentation that the provider and patient have discussed risks of myeloablative treatment on future fertility and options for fertility-preservation?	Yes: Approve for one lifetime dose	No: Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 6/24 (SF)
 Implementation: TBD