Anthem

# Medical Policy

**Subject:** Gene Therapy for Sickle Cell Disease
**Document #:** MED.00146
**Status:** Revised

**Publish Date:** 01/30/2025
**Last Review Date:** 08/08/2024

## Description/Scope

This document addresses gene therapy for sickle cell disease (SCD) which is a genetic disease involving variations in the human beta-globin gene (HBB) that reduce an individual's ability to produce functional hemoglobin leading to a shortage of mature red blood cells and a lack of sufficient oxygen circulation. The characteristic sickle-shaped red blood cells are rigid and can block small blood vessels (vaso-occlusion), causing severe pain and organ damage.

Two hematopoietic stem cell-based gene therapy products have been approved by the U.S. Food and Drug Administration (FDA) to treat SCD, exagamglogene autotemcel (Casgevy™) and lovotibeglogene autotemcel (Lyfgenia®). In Casgevy therapy, the BCL11A gene, which encodes a repressor of fetal hemoglobin (HbF) levels, is edited in an individual's own hematopoietic stem cells using the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) nuclease system to produce high levels of HbF in red blood cells. Lyfgenia therapy involves using a modified lentivirus to deliver a functional copy of the beta-globin HBB gene to the individual's cells. Both therapies produce functional hemoglobin proteins that may compensate for defective beta-globin, thereby reducing painful and debilitating sickle cell crises for those with SCD.

**Note:** Please see the following related documents for additional information:

- CG-MED-90 Chelation Therapy
- MED.00140 Gene Therapy for Beta Thalassemia

## Position Statement

**Medically Necessary:**

A one-time infusion of exagamglogene autotemcel is considered **medically necessary** in individuals when **all** of the following criteria are met:

A. Diagnosis of sickle cell disease; **and**
B. At least 4 severe vaso-occlusive crises in the previous 2 years; **and**
C. 12 years of age and older; **and**
D. Hydroxyurea therapy failure or intolerance; **and**
E. The individual is a candidate for an allogeneic hematopoietic cell transplantation, but ineligible due the absence of a donor*; **and**
F. No serious concomitant illness (for example, advanced liver disease, clinically significant active infection, severe cerebral vasculopathy, clinically significant pulmonary hypertension, inadequate pulmonary or cardiac function, prior or current malignancy other than previously treated non-life-threatening tumors, immunodeficiency disorder); **and**
G. No prior receipt of gene therapy.

A one-time infusion of lovotibeglogene autotemcel is considered **medically necessary** in individuals when **all** of the following criteria are met:

A. Diagnosis of sickle cell disease; **and**
B. At least 4 severe vaso-occlusive crises in the previous 2 years; **and**
C. 12 years of age and older; **and**
D. Hydroxyurea therapy failure or intolerance; **and**

E. The individual is a candidate for an allogeneic hematopoietic cell transplantation, but ineligible due the absence of a donor*; **and**
F. No serious concomitant illness (for example, advanced liver disease, clinically significant active infection, severe cerebral vasculopathy, clinically significant pulmonary hypertension, inadequate pulmonary or cardiac function, prior or current malignancy other than previously treated non-life-threatening tumors, immunodeficiency disorder) **and**
G. No prior receipt of gene therapy.

*Documentation that a suitable donor has not been identified, for example, a matched related donor or matched (HLA 8/8 or 7/8) unrelated donor.

Autologous hematopoietic stem cell mobilization and pheresis is considered **medically necessary** prior to exagamglogene autotemcel or lovotibeglogene autotemcel infusion when the criteria above have been met.

**Investigational and Not Medically Necessary:**

Gene therapy for sickle cell disease is considered **investigational and not medically necessary** when the criteria above are not met.

## Rationale

*Viral vector gene therapy*

Gene therapy for sickle cell disease involves extraction of CD34+ stem cells from the affected individual's bone marrow or blood using a process called pheresis. The collected stem cells are the genetically modified *ex vivo* with a lentiviral vector encoded with functional DNA. The individual then undergoes myeloablative conditioning followed by infusion of the modified stem cells into the individual intravenously during an autologous hematopoietic stem-cell transplant procedure. Mobilization, pheresis, myeloablation, and stem cell transplantation procedures are necessary components of this type of gene therapy.

*Exagamglogene autotemcel*

Adult hemoglobin consists of two alpha chains and two beta chains while HbF consists of two alpha and two gamma chains. The gamma-globin gene (HBG) encoding the gamma chain is developmentally regulated, normally being expressed only in utero and during infancy. During this early time of life, the HBB gene encoding beta-globin is expressed at very low levels because the red blood cells have not yet shifted from expression of HBG to expression of the HBB gene, a phenomenon known as hemoglobin switching (Sankaran, 2013). Thus, infants with SCD are typically free of clinical symptoms while their HbF levels remain high, and become symptomatic during the first year of life when the synthesis of HbF declines and adult hemoglobin predominates. Elevated levels of HbF are associated with improved morbidity and mortality in individuals with SCD (Powars, 1984). Likewise, individuals with SCD who co-inherit hereditary persistence of HbF, in which fetal expression continues into adulthood, have little or no disease (Steinberg, 2020).

BCL11A is a transcription factor that represses HBG gene expression in red blood cells, and therefore lowers HbF production, starting in infancy (Bauer, 2015). Conversely, downregulation of BCL11A increases the production of HbF (Sankaran, 2008). CRISPR-Cas9 gene-editing techniques in hematopoietic stem and progenitor cells (HSPCs) have been used to reduce BCL11A expression in red blood cells, restore gamma-globin synthesis, and reactivate production of HbF (Frangoul, 2021). The goal of this technology is to alleviate the symptoms of SCD by substituting HbF for the faulty adult hemoglobin.

Exagamglogene autotemcel, or exa-cel (formerly known as CTX001), is composed of autologous CD34+ HSPCs modified with CRISPR-Cas9 at the red blood cell-specific enhancer region of the BCL11A gene in order to reduce BCL11A expression. To manufacture exa-cel, blood cells are first collected from an affected individual by apheresis, then shipped to the manufacturing site under controlled conditions (Frangoul, 2021). Next, CD34+ HSPCs are isolated from the blood cells. Then CRISPR-Cas9 technology is employed to edit the BCL11A gene in the CD34+ HSPCs. The CRISPR ribonucleoprotein complex (RNP) is prepared by mixing guide RNA (genetic material that helps target the editing location) and purified Cas9 protein (CRISPR's genetic "scissors"). The RNP mixture is introduced into the CD34+ HSPCs by electroporation. After electroporation, the cells are incubated in culture medium, at which time the CRISPR-Cas9 process takes place: the guide RNA seeks out the target gene and Cas9 cuts it, creating a deliberate change in the gene that results in decreased production of the BCL11A protein. The modified cells are then cryo-preserved in liquid nitrogen. After quality control procedures are completed to determine cell purity, on-target editing frequency and cell viability, the frozen

cell suspension is shipped back to the clinical site. Individuals from whom exa-cel is prepared receive single-agent busulfan myeloablation before receiving exa-cel in order to suppress the ability of bone marrow to produce native blood cells. The individuals are then infused with autologous exa-cel product consisting of over a million modified CD34+ HSPCs per kilogram of body weight.

Although the target gene specificity of the CRISPR-Cas nuclease is determined by the guide RNA, Cas proteins can also bind and cleave partially complementary unintended locations not targeted ("off-target effects"), raising safety concerns for their use in clinical applications (Tao, 2023). This problem is especially important since the effects of gene editing agents are permanent. Evidence has been reported of laboratory examples of CRISPR-Cas9 gene editing resulting in genetic damage as a consequence of off-target editing (Kosicki, 2018).

In the single published case report detailing the use of exa-cel gene editing technology to treat human SCD, preclinical on-target and off-target editing analyses were performed in CD34+ HSPCs obtained from 10 healthy donors (Frangoul, 2021). High frequencies of allelic editing (mean ± SD, 80 ± 6%) were observed across all subpopulations of CD34+ cells, including long-term hematopoietic stem cells. Potential sites of off-target editing were identified using sequence similarity (computational) and laboratory-based methods by means of genome-wide unbiased identification of double-stranded breaks enabled by sequencing (GUIDE-seq). In edited CD34+ cells obtained from 4 healthy donors, potential off-target sites were evaluated with the use of high-coverage, hybrid-capture experiments by means of deep next-generation sequencing. No evidence of off-target editing was found. However, a serious limitation of this approach is that these studies were done on cells from healthy donors rather than on the clinical samples used for treatment of affected individuals.

In this study, one person with beta thalassemia and one person with SCD were treated (Frangoul, 2021). Eligibility was limited to people who were between the ages of 18 and 35 years. Individuals with SCD could participate if they had a documented βS/βS or βS/β0 genotype and had a history of 2 or more severe vaso-occlusive episodes per year during the previous 2 years. Key exclusion criteria included availability of a willing and healthy 10/10 Human Leukocyte Antigen (HLA)-matched related donor, and prior allogenic hematopoietic stem cell transplantation.

After undergoing exa-cel preparation and myeloablation, each subject received autologous exa-cel. More than a year later, both individuals had high levels of allelic editing in bone marrow and blood (76-80% and 62-64%, respectively), increases in HbF (from 9% to 43% in the participant with SCD), and elimination of vaso-occlusive episodes. The clinical course of both subjects was similar to the phenotype of hereditary persistence of HbF levels.

Adverse events were reported in both subjects after the exa-cel infusion. The serious adverse events that were observed were pneumonia in the presence of neutropenia, veno-occlusive liver disease with sinusoidal obstruction syndrome, sepsis in the presence of neutropenia, cholelithiasis, and abdominal pain. The nonserious adverse event of lymphopenia was also observed.

In a presentation of preliminary data to the Congress of the European Hematology Association, early results from the CLIMB SCD-121 (NCT03745287) trial were reported (Locatelli, 2022). CLIMB SCD-121 is a Phase I/II/III study of the safety and efficacy of a single dose of exa-cel in subjects with severe SCD. Data from 31 participants with SCD who were dosed with exa-cel were reported. Mean follow-up was 9.6 (range 2.0-32.3) months. All participants with SCD no longer had severe vaso-occlusive episodes (duration 2.0-32.3 months). The mean proportion of HbF in SCD participants was > 20% by month 3, increasing to approximately 40% at month 4, and was stable thereafter, with mean total Hb levels > 11 g/dL after month 3, close to the normal range in children (11-15 g/dL). All subjects with at least 1 year of follow-up had stable proportions of edited BCL11A alleles in bone marrow CD34+ HSPCs and peripheral blood mononuclear cells. There were no serious adverse events considered related to exa-cel. There were no deaths, discontinuations, or malignancies although this study is limited by the short duration of follow-up.

For the CLIMB SCD-121 trial (NCT03745287), key inclusion criteria consisted of the following:

- Individuals 12 years to 35 years of age.
- Diagnosis of severe SCD as defined by:
    - Documented severe SCD genotype.
    - History of at least 2 severe vaso-occlusive crisis (VOC) events per year for the previous 2 years prior to enrollment. Severe VOC is defined as an occurrence of at least one of the following events:
        - Acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or intravenous [IV] non-steroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions
        - Acute chest syndrome
        - Priapism lasting > 2 hours and requiring a visit to a medical facility

    - Splenic sequestration
- Eligible for autologous stem cell transplant as per investigator's judgment.

Key exclusion criteria for the CLIMB SCD-121 trial included the following:

- A willing and healthy 10/10 HLA-matched related donor is available per investigator's judgement.
- Prior HSCT.
- Clinically significant and active bacterial, viral, fungal, or parasitic infection.

In addition to the studies discussed above, other clinical trials are ongoing but do not yet have published results:

- NCT05329649 is a single-dose, open-label study in pediatric participants with severe SCD and hydroxyurea failure or intolerance. The study will evaluate the safety and efficacy of autologous CRISPR-Cas9 modified CD34+ hHSPCs (CTX001). The primary outcome is the proportion of participants who do not have any severe vaso-occlusive crises for at least 12 consecutive months.
- NCT05477563 is a single-dose, open-label study in participants with transfusion-dependent β-thalassemia or severe SCD. The study will evaluate the safety and efficacy of autologous CRISPR-Cas9 modified CD34+ human hematopoietic stem and progenitor cells (hHSPCs) using CTX001 (exa-cel). Primary outcome measures are HbF and total hemoglobin concentrations over time.

Exagamglogene autotemcel (Casgevy) was approved by the FDA on December 8, 2023 for the treatment of individuals 12 years of age or older with SCD and a history of vaso-occlusive events. As in the CLIMB SCD-121 trial, individuals must be judged to be clinically eligible for autologous stem cell transplant. The product insert states that prior to Casgevy infusion it must be confirmed that HSCT is appropriate for the individual before mobilization, apheresis and myeloablative conditioning are initiated. The product was approved for single intravenous administration only; repeat administration of Casgevy and its use for the treatment of other indications has not been evaluated.

FDA approval was based on unpublished findings of Casgevy use in 31 adult and adolescent individuals with SCD in an ongoing single-arm, multi-center trial (CLIMB SCD-121). The primary outcome was the proportion of individuals who did not experience any severe vaso-occlusive crises (VOCs) for at least 12 consecutive months within the first 24 months after Casgevy infusion. This outcome was achieved in 29/31 individuals (93.5%). Of the 29 participants who responded to the treatment, none experienced severe VOCs during the evaluation period with a median duration of 22.2 months at the time of the analysis. The mean proportion of hemoglobin comprised by HbF was 43.9% at Month 6 and was maintained thereafter up to 24 months. All treated individuals achieved successful engraftment with no individuals experiencing graft failure or graft rejection.

In 2024, Frangoul and colleagues published results from 44 individuals with SCD who received exa-cel treatment in the CLIMB SCD-121 trial (NCT03745287). The median follow-up time was 19.3 months. Of the 30 individuals who had sufficient follow-up to be evaluated, 29 (97%) met the primary endpoint which was freedom from severe VOCs for ≥ 12 consecutive months; all 30 (100%) were free from hospitalizations for VOCs for at least 12 consecutive months ($p<0.001$ for both comparisons against the null hypothesis of a 50% response). Among the 29 individuals who were free from VOCs for at least 12 consecutive months, the mean duration of freedom from VOCs was 22.4 months (range 14.8 to 45.5). The mean (±SD) percentage of HbF was 36.9 ± 9.0% at 3 months, increased to 43.9 ± 8.6% at 6 months, and was at least 40% during follow-up. The mean total hemoglobin level was 11.9 ± 1.5 g/dL at 3 months, 12.5 ± 1.8 g/dL at 6 months, and thereafter, the total hemoglobin values were maintained at normal or near-normal levels (normal range, 12.1 to 17.2 g/dL). Among all participants, the mean percentage of edited BCL11A alleles in peripheral blood cells was 53.5% at 1 month and was at least 70% from 2 months through the end of follow-up. Exa-cel treatment was generally found to be safe, with a profile consistent with that of myeloablative busulfan conditioning and autologous HSPC transplantation. No participants developed graft failure or cancer. A long-term follow-up study (CLIMB-131; NCT04208529) is continuing to monitor total hemoglobin, HbF levels and safety of exa-cel in individuals who have completed the CLIMB SCD-121 study.

In summary, SCD is a condition associated with extensive morbidity and early mortality. Gene editing therapy with exa-cel has the potential to delay disease progression with a single treatment, and possibly provide long-term relief from symptoms. The available peer-reviewed literature on the use of exa-cel as a gene-editing therapy SCD is limited to 2 reports (Frangoul, 2021; Frangoul, 2024). However, the FDA has determined that the data support the use of exa-cel for treatment of individuals with severe SCD who are candidates for allogeneic hematopoietic cell transplantation, but who lack a suitable donor and when serious concomitant illness is not present. While the therapy is considered potentially curative, long-term data on both safety and effectiveness are lacking (median length of follow-up in the 2024 study is 19.3 months). Theoretical safety concerns include, but are not limited to the host’s immune response to the gene-editing therapy, potential risk of blood cancer, and unintended off-target mutations.

*Lovotibeglogene autotemcel*

Lovotibeglogene autotemcel gene therapy, also known as lovo-cel or Lentiglobin, is a one-time treatment for SCD that is designed to insert a functioning version of the HBB gene into the DNA of an individual's own stem cells. This is accomplished by retrieving stem cells from an individual's blood, engineering them outside of the body using a modified virus (lentivirus vector) to add functional copies of a form of HBB (βA-T87Q-globin gene), and then transplanting the cells back into the body. Once individuals have the βA-T87Q-globin gene, their red blood cells can produce anti-sickling hemoglobin (HbAT87Q) that decreases the proportion of HbS (sickle hemoglobin), with the goal of reducing sickled red blood cells, hemolysis, and other complications.

Treatment with lovo-cel involves the following steps (Kanter, 2023):

1. Pre-collection preparation and collection of autologous hematopoietic stem and progenitor cells (HSPCs)
2. Lovo-cel manufacturing via the ex vivo transduction of autologous HSPCs with the BB305 LVV (lentivirus vector) containing the βA-T87Q transgene
3. Myeloablative conditioning
4. Lovo-cel infusion
5. Engraftment of HSPCs leading to the production of an anti-sickling hemoglobin, HbAT87Q

FDA approval was based on findings of the Phase I/II HGB-206 study evaluating Lentiglobin for sickle cell disease (NCT02140554); findings were published by Kanter and colleagues in 2022 and 2023. Study inclusion criteria included the following:

- Between 12 and 50 years old,
- Diagnosis of sickle cell disease with a βS /βS , βS /β0 , or βS /β+ genotype,
- Severe disease, specified as in the Kanter (2022) Supplemental Appendix:
- In the setting of appropriate supportive care measures (e.g., pain management plan), have experienced at least 4 severe vaso-occlusive events (VOEs) in the 24 months prior to enrollment as defined below. For the purposes of this study, a severe VOE is defined as an event with no medically determined cause other than a vaso-occlusion, requiring a ≥24-hour hospital or emergency room (ER) observation unit visit, or at least 2 visits to a day unit or ER over 72 hours, with both visits requiring intravenous treatment. Exception: priapism does not require hospital admission but does require a medical facility visit; 4 priapism episodes that require a visit to a medical facility (without inpatient admission) are sufficient to meet criterion. Severe VOEs include:
    a. An episode of acute pain with no medically determined cause other than a VOE.
    b. Acute chest syndrome (ACS), defined by an acute event with pneumonia-like symptoms (e.g., chest pain, fever [>38.5°C], tachypnea, wheezing or cough, or findings upon lung auscultation) and the presence of a new pulmonary infiltrate consistent with ACS, and requiring oxygen treatment and/or blood transfusion.
    c. Acute hepatic sequestration, defined by a sudden increase in liver size associated with pain in the right upper quadrant, abnormal results of liver function test not due to biliary tract disease, and reduction in Hb concentration by ≥2 g/dL below the baseline value.
    d. Acute splenic sequestration, defined as sudden enlargement of the spleen and reduction in Hb concentration by ≥2 g/dL below the baseline value.
    e. Acute priapism: Defined as a sustained, unwanted painful erection lasting more than 2 hours and requiring care at a medical facility (with or without hospitalization).
- 24-month history of active treatment of sickle cell disease.
- Clinically stable Karnofsky performance status of at least 60 (for patients ≥16 years of age) or a Lansky performance status of at least 60 (for those <16 years of age) (both scales range from 0 to 100).
- Failure of hydroxyurea treatment.
- No opportunity for matched HLA-identical hematopoietic-cell donation.

According to the study's supplemental appendix, the following are notable exclusion criteria:

- Positive for presence of active HIV-1 or HIV-2, hepatitis B (HBV), hepatitis C (HCV), human T-lymphotrophic virus-1 or -2, or active syphilis.
- Clinically significant, active bacterial, viral, fungal, or parasitic infection, as determined by the investigator, e.g., active relapsing malaria.
- Inadequate bone marrow function, as defined by an absolute neutrophil count of < $1x10^9$/L, (<$0.5x10^9$/L for subjects on HU treatment) or a platelet count <$100x10^9$/L.

- Severe cerebral vasculopathy, defined by any history of: overt ischemic or hemorrhagic stroke, abnormal transcranial Doppler (TCD >200 cm/sec) requiring chronic transfusion, occlusion or stenosis in the circle of Willis, or presence of Moyamoya disease. Subjects with radiologic evidence of silent infarction in the absence of any of the above criteria would still be eligible.
- Inadequate respiratory reserve as demonstrated by baseline oxygen saturation <90% without supplemental oxygen (excluding periods of sickle cell disease crisis, severe anemia, or infection); and baseline carbon monoxide diffusing capacity (DLCO) < 50% (corrected for Hb) in the absence of infection.
- Baseline left ventricular ejection fraction < 45% measured by cardiac echography.
- Clinically significant pulmonary hypertension at baseline, as defined by the requirement for ongoing pharmacologic treatment or the consistent or intermittent use of supplemental home oxygen.
- Baseline estimated glomerular filtration rate < 70 mL/min/1.73 m2.
- Advanced liver disease. For subjects who have history of iron overload or serum ferritin levels >1000 ng/mL, a cardiac MRI is required. Cardiac T2* < 10 ms results in exclusion.
- Any prior or current malignancy or immunodeficiency disorder, except previously treated, non-life threatening, cured tumors such as squamous cell carcinoma of the skin.
- Prior receipt of an allogeneic transplant.
- Pregnancy, or breastfeeding in a postpartum female, or absence of adequate contraception for fertile subjects.
- Prior receipt of gene therapy.
- Any condition or contraindication that would render the subject ineligible for hematopoietic stem cell transplantation, as determined by the attending transplant physician.
- Applicable to subjects < 18 years of age only: Availability of a willing, matched human leukocyte antigen-identical sibling hematopoietic cell donor.

The treatment process was modified during the study and enrollees were retrospectively designated to 3 sequentially enrolled cohorts. Group A consisted of the first 7 enrollees; these individuals had suboptimal expression of HbAT87Q. For Group B, the next 2 enrollees, the manufacturing process of lovo-cel was refined and the myeloablative conditioning dose was increased and the Lentiglobin cell dose was increased to ≥ 2.0 X $10^6$ CD34+ cells/kg. In Group C, which included 35 individuals, the eligibility criteria were changed to requiring a minimum of 4 severe VOEs in the 24 months before enrollment. In Group C, the Lentiglobin cell dose was further increased to ≥ 3.0 X $10^6$ CD34+ cells/kg.

The intention-to-treat analysis included all individuals who had undergone any study procedure, including stem-cell collection. The per protocol analysis included a sub-analysis that was done of the 29 individuals within Group C in the transplant population with vaso-occlusive events (TPVOE) (at least 4 in the previous 24 months).

After treatment, the vector copy number in peripheral blood remained stable in all individuals between 6 months and the last study visit (for up to 36 months); this indicated persistence of vector-positive, repopulating HSPCs capable of production of HbAT87Q. Median total hemoglobin value increased from 8.5 g per deciliter at baseline to 11.0 g or more per deciliter at 6 to 36 months, and HbAT87Q contributed to at least 40% of total hemoglobin. Sickle hemoglobin levels were approximately 30-40% at baseline in the individuals with sickle trait (βS /βA), and were 50% at 6-36 months post-infusion.

The primary efficacy endpoint was complete resolution of VOEs, assessed at 6 months and 18 months after Lentiglobin infusion. A VOE was defined as acute pain (e.g., acute chest pain, acute hepatic sequestration, acute splenic sequestration and acute priapism) with no other medically determined cause. Severe VOEs resulted in a visit to a hospital or emergency department that lasted more than 24 hours, at least two visits to a medical facility or emergency department during a 72-hour period (both visits had to involve intravenous treatment), or a priapism episode lasting more than 2 hours that led to a medical facility visit.

Among the 25 individuals in the TPVOE group who had at least 6 months of follow-up in the Kanter publications, 3 (12%) had VOEs after infusion. No severe VOEs were reported; this compared with a median rate of 3.5 per year (range, 2.0 to 13.5) in the 24 months before enrollment.

Lovotibeglogene autotemcel (Lyfgenia) was approved by the FDA on December 8, 2023 for the treatment of individuals 12 years of age or older with sickle cell disease and a history of vaso-occlusive events. As in the HGB-206 trial (Kanter, 2023), individuals must be judged to be medically eligible to undergo HSCT. The product insert states that prior to Lyfgenia infusion it must be confirmed that HSCT is appropriate for the individual before mobilization, apheresis and myeloablative conditioning are initiated. The product was approved for single intravenous administration only; repeat administration of Lyfgenia and its use for the treatment of other indications have not been evaluated.

The data presented in the FDA product insert has a median (minimum, maximum) duration of follow-up for participants in the Phase I/II study of 38 (12, 61) months post-infusion. (The FDA materials report a total of 36 individuals in the transplant group whereas the Kanter publications report a total of 35 individuals). Regarding data on the primary efficacy outcomes in the FDA materials, 28 of 32 evaluable individuals (88%) had complete resolution of VOEs between 6 and 18 months post-infusion and 30 of 32 individuals (94%) had complete resolution of severe VOEs. After the primary evaluation period, 4 of 32 individuals experienced VOEs.

All study participants were evaluated for globin response. A total of 31 of 36 individuals (86%) achieved globin response, and all of the individuals who achieved globin response maintained it to the last follow-up. Globin response was defined as meeting both of the following criteria for at least 6 months after infusion:

- Weighted average hemoglobin AT87Q percentage of non-transfused total Hb ≥ 30% AND
- Weighted average non-transfused total Hb (HbS+HbF+HbA2+HbAT87Q) increase of ≥ 3 g/dL compared to baseline total Hb OR weighted average non-transfused total Hb ≥ 10 g/dL.

According to the Kanter publications, a total of 12 of the 35 enrolled individuals (34%) had at least one SAE after Lentiglobin infusion. The most common SAEs were abdominal pain, drug withdrawal syndrome, nausea and vomiting (6% each). A total of 3 individuals had an SAE that was deemed by investigators to be associated with Lentiglobin infusion; 2 were considered possibly related (a case of grade 2 leukopenia and a case of grade 1 decreased diastolic blood pressure) and 1 event that was considered definitely related (grade 2 febrile neutropenia). These 3 events resolved within a week of their onset. One death occurred 20 months after infusion in a 27-year-old individual who had cardiopulmonary disease related to sickle cell disease at baseline and died after cardiac arrest.

Two cases of acute myeloid leukemia were reported 3 years and 5.5 years after Lentiglobin infusion (Goyal, 2022; Kanter, 2022). Upon further investigation of the second case (Goyal, 2022), it was included that development of the condition was likely unrelated to insertional oncogenesis related to Lentiglobin treatment. However, part of the reason for alterations of the treatment protocol for Group C was to reduce the risk of post-transplantation hematologic cancers.

The FDA approval announcement includes cautionary text addressing concerns of risk of insertional oncogenesis.

The Lyfgenia product label includes a black box warning regarding hematologic malignancy, stating the following: “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.”

In summary, available data from a Phase I/II trial support lovotibeglogene autotemcel for treatment of individuals with severe sickle cell disease who are candidates for an allogeneic hematopoietic cell transplantation, but who lack a suitable donor and when serious concomitant illness is not present. Modified eligibility criteria of the Phase I/II trial specified that severe disease required a minimum of 4 severe VOEs in the 24 months before enrollment. While the therapy is considered potentially curative, no Phase III trial was conducted and long-term data on both safety and effectiveness are lacking (median follow-up was 38 months and the longest follow-up was 61 months). Over ten percent of participants in the Lyfgenia trial failed to have complete resolution of VOEs between 6 and 18 months post-infusion, and 4 individuals who achieved complete resolution experienced VOEs after the primary efficacy evaluation. As with other gene therapies, long-term safety remains unknown, including a potential risk of blood cancer.

## Background/Overview

The most common form of SCD is sickle cell anemia (also called homozygous sickle cell disease or HbSS disease). This form is caused by a single nucleotide variation in the HBB gene that replaces glutamic acid with valine in beta-globin at amino acid position 6. The abnormal beta-globin produced is called hemoglobin S or HbS. Replacing glutamic acid with valine causes HbS subunits to stick together and form long, rigid molecules that distort red blood cells into a sickle shape. The sickle-shaped cells are more fragile and die more quickly than normally shaped cells, leading to a shortage of red blood cells (anemia). The sickle-shaped cells are rigid and can block small blood vessels (vaso-occlusion), causing severe pain and organ damage.

Symptoms of SCD usually begin in early childhood. The disease is characterized by a low number of red blood cells (anemia), repeated infections, and periodic episodes of pain. Yellowing of the eyes and skin, which are signs of jaundice, may also be present due to the rapid breakdown of red blood cells. Vaso-occlusive episodes can lead to organ damage if tissues and organs, such as the lungs, kidneys, spleen, and brain, are deprived of oxygen-rich blood. A particularly serious

complication of SCD is pulmonary hypertension, high blood pressure in the blood vessels that supply the lungs, which can lead to heart failure. About 10% of adults with SCD have pulmonary hypertension.

SCD is inherited in an autosomal recessive manner. Individuals affected with SCD have two copies of the gene with the sickle variant in each cell (βS/βS genotype). Individuals with one sickle cell gene and one that produces no detectable beta-globin (βS/β0 genotype) may also be affected with SCD. Individuals with one altered copy of the gene and one normal copy are generally asymptomatic.

SCD is among the most prevalent inherited monogenic disorders, affecting more than 20 million people worldwide and approximately 100,000 Americans. It is most common among people whose ancestors come from Africa, India, Mediterranean countries, the Arabian Peninsula, and Spanish-speaking regions in South and Central America and the Caribbean. SCD is estimated to occur in 1 in 500 African Americans, and 1 in 1000 to 1400 Hispanic Americans.

SCD is diagnosed by blood tests to check for HbS by hemoglobin electrophoresis or HPLC. SCD is also on the list of core newborn screening tests recommended by the U.S. government (Health Resources and Services Administration, 2023).

Treatment for individuals with SCD primarily consists of pain management, blood transfusion, and hydroxyurea. Transfusion increases the number of normal red blood cells which helps reduce symptoms and prevent complications, such as stroke and anemia, in people with SCD. However, undergoing regular transfusions can cause iron overload further requiring chelation therapy to remove the excess iron. Hydroxyurea increases the level of HbF and reduces the tendency for HbS to polymerize, preventing red blood cells from sickling and causing vaso-occlusive episodes. Newborn screening, early treatment interventions, and preventive care have improved survival of individuals with SCD. Nevertheless, the life span of people with SCD is about 20 years shorter than the general population.

The *Evidence-Based Management of Sickle Cell Disease* expert panel report from the National Heart, Lung, and Blood Institute (2014) provides hydroxyurea treatment recommendations for individuals with SCD. A 6 month trial on the maximum tolerated dose is recommended, as a clinical response to treatment with hydroxyurea may take 3-6 months. For individuals who have a clinical response, long-term hydroxyurea therapy is indicated. A lack of increase in red blood cell volume (mean corpuscular volume [MCV]) and/or HbF is not an indication to discontinue therapy. The American Society of Hematology 2020 guidelines for sickle cell disease (DeBaun, 2020) suggest hydroxyurea therapy with at least 20 mg/kg per day at a fixed dose or the maximum tolerated dose in order to prevent cerebrovascular disease in children and adults with SCD.

However, it is estimated that 5-10% of children and 25-30% of adults with SCD have a true lack of efficacy from hydroxyurea (Rodgers, 1990). In addition, some individuals are unable to tolerate even low doses of hydroxyurea due to severe myelosuppression or kidney dysfunction. For individuals who experience hydroxyurea failure or intolerance, treatment options are limited to chronic transfusion therapy, supportive/symptomatic care, or HSCT.

Allogeneic HSCT is a curative treatment currently in use for individuals with SCD. The American Society of Hematology 2021 guidelines for HSCT for SCD (Kanter, 2021) provide recommendations for individuals with SCD and health care professionals to support their decision making. The recommendations are presented in terms of the primary SCD-related complications of concern, the age of the individual, and the type of transplantation under discussion. If HSCT is performed in a center with experience using a matched sibling donor, overall survival is currently close to 100% and event-free survival is over 90% (Bhatia, 2015). However, less than 20% of eligible individuals have a related HLA-matched donor (Frangoul, 2021). In addition, there is debate surrounding the use of HSCT in individuals with SCD with less severe symptoms due to risk of complications of HSCT including graft rejection and GVHD.

In December 2023, the FDA approved a one-time single-dose intravenous infusion of Casgevy for the following indication: “CASGEVY is an autologous genome edited hematopoietic stem cell-based gene therapy indicated for the treatment of sickle cell disease (SCD) in patients 12 years and older with recurrent vaso-occlusive crises (VOCs).”

The following warnings and precautions for Casgevy were listed in the product insert:

- Potential Neutrophil Engraftment Failure: Monitor absolute neutrophil counts (ANC) after CASGEVY infusion. Administer rescue cells in the event of neutrophil engraftment failure. (5.1)
- Prolonged Time to 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 uncommon genetic variants cannot be ruled out. (5.4)

In December 2023, the FDA approved a one-time single-dose intravenous dose of Lyfgenia for the following indication: “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.” Limitations of use included the following: “Following treatment with LYFGENIA, patients with α-thalassemia trait (-α3.7/-α3.7) 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.”

The following warnings and precautions for Lyfgenia were listed in the product insert:

- 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)

*Psychological readiness for gene therapy*

In 2024, the Cure Sickle Cell Initiative, funded by the National Heart, Lung, and Blood Institute, published recommendations to support patient readiness and resilience for gene therapy in sickle cell disease (Hardy, 2024). The recommendations were developed by a working group comprised of behavioral health clinicians and scientists with expertise in SCD as well as adults with SCD. The objective of the working group was to develop consensus recommendations regarding the assessment of psychosocial readiness in the context of gene therapy for SCD. The group identified 5 overarching goals of a pregene therapy patient readiness assessment:

1. Gathering information about a patient’s understanding of and perceived readiness for gene therapy.
2. Encouraging open dialogue regarding any concerns about gene therapy.
3. Providing a conceptualization of psychosocial factors likely to influence participation in gene therapy and affect relevant outcomes.
4. Identifying patient strengths that can be leveraged to promote psychosocial well-being before, during, and after gene therapy.
5. Identifying psychosocial risks to be considered and addressed through tailored education, psychosocial support, and community resources.

Assessment results may help inform individuals’ treatment decisions and guide the delivery of support to enhance readiness.

## Definitions

Allogeneic: Tissue or cells taken from different individuals from the same species.

Apheresis: A procedure by which blood is removed from the body, separated into components, manipulated and returned to the individual.

Autologous: Referring to cells or tissues obtained from the same individual.

Autosomal recessive disorder: An inherited condition for which two copies of an abnormal gene must be present in order for the disease or trait to develop.

CD34: A protein marker expressed on the surface of hematopoietic stem cells and hematopoietic progenitor cells.

Electroporation: The use of high-voltage electric shocks to introduce nucleic acids and proteins into cells.

Gene editing: A group of technologies that allows genetic material to be added, removed, or altered in a cell.

Gene therapy: A medical treatment that introduces or alters genetic material to replace the function of a missing or dysfunctional gene with the goal of lessening or eliminating a disease process that results from genetic dysfunction.

Graft-versus-host disease (GVHD): The condition that results when the immune cells of a transplant (usually of bone marrow) react against the tissues of the person receiving the transplant.

Hemoglobin switching: The phenomenon of developmental stage-specific expression of globin genes.

Hematopoietic stem cells: Cells that give rise to distinct daughter cells, one cell that replicates the stem cell and one cell that will further proliferate and differentiate into a mature blood cell; also called progenitor cells.

Lentivirus: A genus of retroviruses that can cause slowly progressive diseases; human immunodeficiency virus (HIV) is a type of lentivirus.

Myeloablation: Treatment with a chemotherapy agent that kills cells in the bone marrow.

Myelosuppression: A decrease in bone marrow activity that results in reduced production of blood cells.

## Coding

*The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.*

**When services may be Medically Necessary when criteria are met:**

**CPT**

| | |
|---|---|
| | For the following CPT codes **when related to exagamglogene autotemcel (Casgevy) or lovotibeglogene autotemcel (Lyfgenia) gene therapy**: |
| 38206 | Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous |
| 38232 | Bone marrow harvesting for transplantation; autologous |
| 38241 | Hematopoietic progenitor cell (HPC); autologous transplantation [when specified as infusion of genetically modified stem cell Casgevy or Lyfgenia gene therapy product] |

**HCPCS**

| | |
|---|---|
| J3392 | Injection, exagamglogene autotemcel, per treatment [Casgevy] |
| J3394 | Injection, lovotibeglogene autotemcel, per treatment [Lyfgenia] |

**ICD-10 Procedure**

| | |
|---|---|
| XW133H9 | Transfusion of lovotibeglogene autotemcel into peripheral vein, percutaneous approach, new technology group 9 |
| XW143H9 | Transfusion of lovotibeglogene autotemcel into central vein, percutaneous approach, new technology group 9 |
| XW133J8 | Transfusion of exagamglogene autotemcel into peripheral vein, percutaneous approach, new technology group 8 |
| XW143J8 | Transfusion of exagamglogene autotemcel into central vein, percutaneous approach, new technology group 8 |
| | And for the following codes **when specified as pheresis of autologous cells for Casgevy or Lyfgenia gene therapy:** |
| 6A550ZV | Pheresis of hematopoietic stem cells, single |
| 6A551ZV | Pheresis of hematopoietic stem cells, multiple |

**ICD-10 Diagnosis**

| | |
|---|---|
| D57.00-D57.819 | Sickle-cell disorders |

**When services are Investigational and Not Medically Necessary:**
For the procedure codes listed above when criteria are not met or for all other diagnoses not listed.

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13. Steinberg MH. Fetal hemoglobin in sickle cell anemia. Blood. 2020; 136:2392-2400.
14. Tao J, Bauer DE, Chiarle R. Assessing and advancing the safety of CRISPR-Cas tools: from DNA to RNA editing. Nat Commun. 2023; 14(1):212.

**Government Agency, Medical Society, and Other Authoritative Publications:**

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    - A Gene Transfer Study Inducing Fetal Hemoglobin in Sickle Cell Disease (GRASP, BMT CTN 2001). NCT05353647
    - A Safety and Efficacy Study Evaluating CTX001 in Subjects With Severe Sickle Cell Disease. NCT03745287.
    - A Study Evaluating Gene Therapy With BB305 Lentiviral Vector in Sickle Cell Disease. NCT04293185.
    - A Study Evaluating the Safety and Efficacy of bb1111 in Severe Sickle Cell Disease. NCT02140554.
    - A Study Evaluating the Safety and Efficacy of EDIT-301 in Participants With Severe Sickle Cell Disease (RUBY). NCT04853576.
    - BEACON: A Study Evaluating the Safety and Efficacy of BEAM-101 in Patients With Severe Sickle Cell Disease. NCT05456880.
    - Clinical Study of BRL-101 in Severe. SCD NCT06300723.
    - Clinical Study on the Safety and Efficacy of BRL-101 in the Treatment of Sickle Cell Disease. NCT06287086.
    - Evaluation of Efficacy and Safety of a Single Dose of CTX001 in Participants With Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease. NCT05477563.
    - Evaluation of Efficacy and Safety of a Single Dose of Exa-cel in Participants With Severe Sickle Cell Disease, βS/βC Genotype .NCT05951205.
    - Evaluation of Safety and Efficacy of CTX001 in Pediatric Participants With Severe Sickle Cell Disease (SCD). NCT05329649.
    - Gene Correction in Autologous CD34+ Hematopoietic Stem Cells (HbS to HbA) to Treat Severe Sickle Cell Disease. NCT04819841.
    - Gene Transfer for Sickle Cell Disease. NCT03282656.
    - Long - Term Follow Up of Sickle Cell Disease and Beta-thalassemia Subjects Previously Exposed to BIVV003 or ST-400. NCT05145062.
    - Long-term Follow-up (LTFU) of Patients Treated With Genome-edited Autologous Hematopoietic Stem and Progenitor Cells (HSPC). NCT06155500.
    - Long-term Follow-up of Subjects With Sickle Cell Disease Treated With Ex Vivo Gene Therapy. NCT04628585.

- Safety and Efficacy of Gene Therapy of the Sickle Cell Disease by Transplantation of an Autologous CD34+ Enriched Cell Fraction That Contains CD34+ Cells Transduced ex Vivo With the GLOBE1 Lentiviral Vector Expressing the βAS3 Globin Gene in Patients With Sickle Cell Disease (DREPAGLOBE) (DREPAGLOBE). NCT03964792.
- Stem Cell Gene Therapy for Sickle Cell Disease. NCT02247843.
- Study of Safety and Efficacy of Genome-edited Hematopoietic Stem and Progenitor Cells in Sickle Cell Disease (SCD). NCT04443907.
- A Long-term Follow-up Study in Participants Who Received CTX001. NCT04208529.

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**Conference Abstract**

1. Locatelli F. Efficacy and safety of a single dose of CTX001 for transfusion-dependent beta-thalassemia and severe sickle cell disease [conference presentation abstract]. In: Congress of the European Hematology Association; June 9-17, 2022; Vienna, Austria. Available at: EHA Library - The official digital education library of European Hematology Association (EHA). Accessed on June 20, 2024.


## Websites for Additional Information


1. Sickle Cell Disease Association of America. https://www.sicklecelldisease.org. Accessed on June 20, 2024.
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## Index



**The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.**

## Document History

| Status | Date | Action |
|---|---|---|
| | 01/30/2025 | Updated Coding section with 01/01/2025 HCPCS changes, added J3392, removed NOC codes C9399, J3490, J3590 no longer applicable. |
| Revised | 08/08/2024 | Medical Policy & Technology Assessment Committee (MPTAC) review. Added new MN statement regarding autologous hematopoietic stem cell mobilization and |

| | | |
|---|---|---|
| | | pheresis. Revised Description, Rationale, References, and Websites sections. Revised Coding section, added stem cell related codes 38206, 38232, 38241, 6A550ZV, 6A551ZV. |
| | 06/28/2024 | Updated Coding section with 07/01/2024 HCPCS changes; added J3394 replacing NOC codes for Lyfgenia. |
| New | 01/16/2024 | MPTAC review. Initial document development. |
| Preliminary Discussion | 05/11/2023 | MPTAC pre-FDA approval review. |

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Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.