Anthem

Medical Policy

Subject: Gene Therapy for Beta Thalassemia
Document #: MED.00140
Status: Revised

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

Description/Scope

This document addresses gene therapy for beta thalassemia, a genetic disease that involves mutations in the human beta-globin (HBB) gene. These mutations reduce an affected individual's ability to produce hemoglobin and lead to a shortage of mature red blood cells and a lack of sufficient oxygen. There are several types of gene therapy proposed for treatment of beta thalassemia. Viral vector gene therapy involves using a modified virus to deliver a functional copy of the beta-globin gene to the patient's cells. Gene editing therapy uses molecular tools to directly modify the individual's DNA in order to correct for the underlying genetic defects that result in beta hemoglobinopathy.

Two gene therapy products for beta thalassemia have been approved by the Food and Drug Administration (FDA): betibeglogene autotemcel (Zynteglo®) and exagamglogene autotemcel (Casgevy™). Please see MED.00146 Gene Therapy for Sickle Cell Disease for use of Casgevy in the treatment of sickle cell disease. Both Zynteglo and Casgevy are autologous hematopoietic stem cell-based gene therapies that require individuals to undergo hematopoietic stem cell (HSC) mobilization followed by apheresis to obtain CD34+ cells for manufacturing, as well as administration of full myeloablative conditioning before infusion.

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

- CG-MED-90 Chelation Therapy
- MED.00146 Gene Therapy for Sickle Cell Disease

Position Statement

Medically Necessary:

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

A. Diagnosis of beta thalassemia; **and**
B. Transfusion-dependent disease (that is, needing at least 8 transfusions or at least 100 ml per kilogram of body weight of packed red cells per year in the previous 2 years); **and**
C. The individual is a candidate for an allogeneic hematopoietic cell transplantation, but ineligible due the absence of a donor*; **and**
D. Has no evidence of severe iron overload (for example, T2*-weighted magnetic resonance imaging [MRI] measurements of myocardial iron greater than 10 msec); **and**
E. No serious concomitant illness (for example, advanced liver disease, uncorrected bleeding disorder, current malignancy, myeloproliferative and/or immunodeficiency disorder, uncontrolled seizure disorder).

*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.

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

A. Diagnosis of beta thalassemia; **and**
B. 12 years of age or older; **and**
C. Transfusion-dependent disease (that is, needing at least 8 transfusions or at least 100 ml per kilogram of body weight of packed red cells per year in the previous 2 years); **and**

D. The individual is a candidate for an allogeneic hematopoietic cell transplantation, but ineligible due the absence of a donor*; **and**
E. Has no evidence of severe iron overload (for example, T2*-weighted magnetic resonance imaging [MRI] measurements of myocardial iron greater than 10 msec); **and**
F. No serious concomitant illness (for example, advanced liver disease, uncorrected bleeding disorder, current malignancy, myeloproliferative and/or immunodeficiency disorder, uncontrolled seizure disorder).

*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 betibeglogene autotemcel infusion when the criteria above have been met.

Investigational and Not Medically Necessary:

Gene therapy for beta thalassemia is considered **investigational and not medically necessary** when the criteria above are not met.

Rationale

Viral vector gene therapy

Gene therapy for beta thalassemia 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. Hematopoietic stem cell mobilization, pheresis, myeloablation, and stem cell transplantation procedures are necessary components of this type of gene therapy.

Betibeglogene autotemcel

It should be noted that in some of the published clinical trial reports, betibeglogene autotemcel is referred to by the former name, Lentiglobin.

Betibeglogene autotemcel (Zynteglo) was approved by the FDA on August 17, 2022 for the treatment of adult and pediatric patients with beta thalassemia who require regular red blood cell (RBC) transfusions. The product was approved for single intravenous administration only; repeat administration of Zynteglo and its use for the treatment of other indications have not been evaluated.

Approval was based on review of data of two single-arm, open-label, 24-month Phase 3 studies involving a total of 41 subjects aged 4 to 34 years with both non-β0/β0 and β0/β0 beta thalassemia genotypes who were treated with betibeglogene autotemcel. The first study, previously published by Locatelli and colleagues (2022), included 23 individuals aged 50 or younger with transfusion-dependent beta thalassemia and a non-β0/β0 genotype. The study included two cohorts; 15 participants were in the cohort of individuals aged 12 to 50, and 8 participants were in the cohort of individuals younger than 12 years old. The study required transfusion dependence, defined as receipt of at least eight transfusions or at least 100 ml per kilogram kg of body weight of packed red cells per year in the past two years. Exclusion criteria that are identical or similar to those in earlier published Phase I/II studies and included:

- Human immunodeficiency virus infection
- White blood cell (WBC) counts < 3X 10^9/liter (L) and/or platelet counts < 100X 10^9/L (not due to hyperspenism)
- Uncorrected bleeding disorder
- Prior or current malignancy, myeloproliferative and/or immunodeficiency disorder
- Prior hematopoietic stem cell transplant (HSCT)
- Advanced liver disease
- Kidney disease with a baseline estimated glomerular filtration rate < 70 mL/min/1.73 m2
- Uncontrolled seizure disorder
- Cardiac T2* < 10 ms by magnetic resonance imaging or other evidence of severe iron overload
- Diffusion capacity of carbon monoxide (DLco) < 50% predicted
- Test positive for hepatitis B or C (Phase I/II study required active hepatitis B or C infection)
- Immediate family member with a known familial cancer syndrome (Phase I/II study excluded people with either a known or suspected familial cancer syndrome)

Additionally, the Phase III study excluded individuals with the following:

- Clinically significant active bacterial, viral fungal or parasitic infection
- Other condition that would make the individual ineligible for HSCT
- Presence of a known and available HLA-matched family donor for HSCT
- Prior receipt of gene therapy

The primary endpoint was transfusion independence, defined as a weighted average hemoglobin level ≥ 9 grams (g) per deciliter (dL) starting 60 days after the last transfusion, in individuals who had not received red-cell transfusions for ≥ 12 months. A total of 20 of 22 participants (91%) who were available for evaluation met criteria for transfusion independence after a median duration of 20.4 months (range 15.7 to 21.6 months). One participant was not available for evaluation. Mean hemoglobin level during transfusion independence was 11.7 g/dL (range, 9.5 to 12.8). The 2 evaluable individuals who did not attain transfusion independence had 67.4% and 22.7% reductions in transfusion volume, respectively from 6 months to the last follow-up which occurred at 48.2 and 27.2 months, respectively. Eleven of the 20 individuals (55%) who attained transfusion independence restarted iron chelation a median of 7.2 months after betibeglogene autotemcel infusion; 4 of these later discontinued chelation. Additionally, 7 individuals underwent phlebotomy to reduce iron levels. Three individuals did not restart iron chelation or undergo phlebotomy after gene therapy treatment. Among the 23 treated individuals, the most frequent serious adverse events (SAEs) (≥ grade 3) through 2 years of follow-up were thrombocytopenia in 22 (96%), neutropenia in 18 (78%), anemia in 14 (61%), stomatitis in 14 (61%), leukopenia in 13 (57%) and febrile neutropenia in 8 (35%). Three individuals had grade 4 serious hepatic veno-occlusive disease, which was attributed to busulfan-based myeloablation.

The other open-label phase III study, known as HGB-212, is currently ongoing and unpublished. It is intended to evaluate betibeglogene autotemcel in individuals with both β0/β0 and non-β0/β0 genotypes. The study includes 18 participants followed for 24 months to evaluate the efficacy of betibeglogene autotemcel therapy. A subpopulation of 10 participants have been enrolled in a continuation study beyond the 24-month time point. At the time of FDA review, the available data included a median follow-up of 26.6 months, with all participants surviving with no reported case of graft-versus-host disease (GVHD), graft failure, or graft rejection. Transfusion independence was evaluable in 14 participants, with 86% (12/14) achieving transfusion independence with a median weighted average Hb during 10.20 g/dL. All participants maintained transfusion independence, with a minimum and maximum duration 12.5+ and 32.8+ months respectively (n=12). In the 2 individuals who were evaluable for transfusion independence and did not achieve it, a reduction of 92% and 3% in transfusion volume requirements and a reduction of 87% and 21% in transfusion frequency were observed from 6 months post-drug product infusion to last follow-up compared to pre-enrollment requirements. Of the 12 individuals who achieved transfusion independence, 7 were not on chelation therapy as of last follow-up, with 3 (43%) not restarting chelation and 4 (57%) restarting and then stopping iron chelation. Of this latter group the median time from last iron chelation to last follow-up was 7.2 (6.0, 21.4) months. One participant (8%) received phlebotomy to remove iron.

The overall combined data for the two FDA-reviewed studies had a median follow-up of 27.2 months (range 4.1-48.2). Eighty-nine percent of evaluable participants (32/36) achieved transfusion independence. These findings were independent of age or phenotype and were durable as of last follow-up. Serious adverse reactions were reported in 37% of participants, with the most common (> 3%) being pyrexia, thrombocytopenia, liver veno-occlusive disease, febrile neutropenia, neutropenia, and stomatitis. No deaths were reported. All participants achieved neutrophil engraftment. However, 7% of participants remained dependent on G-CSF beyond day 43, and 1 remained dependent through Day 77. The report stated that G-CSF discontinuation was followed by transient decreases in neutrophil counts to less than 500 cells/microliter after day 43 in 6 participants (15%).

Additional data addressing the safety, efficacy, and clinical utility of betibeglogene autotemcel has been published. Findings in individuals with transfusion-dependent beta thalassemia treated with betibeglogene autotemcel from two Phase I/II trials (n=22) were reported in the NEJM by Thompson and colleagues in 2018. A total of 18 individuals from trial HGB-204, who were at least 12 years old, and 4 individuals from trial HGB-205, who were at least 5 years old, underwent myeloablative conditioning with busulfan and were infused with betibeglogene autotemcel. Study participation required transfusion dependence. Key exclusion criteria include the following:

- Human immunodeficiency virus infection
- Active hepatitis B or C infection
- White blood cell (WBC) counts < 3X 10^9/liter (L) and/or platelet counts < 100X 10^9/L (not due to hyperspenism)
- Uncorrected bleeding disorder
- Prior or current malignancy, myeloproliferative and/or immunodeficiency disorder
- Immediate family member with a known or suspected familial cancer syndrome
- Prior HSCT

- Advanced liver disease
- Kidney disease with a baseline estimated glomerular filtration rate < 70 mL/min/1.73 m2
- Uncontrolled seizure disorder
- Clinically significant pulmonary hypertension
- Diffusion capacity of carbon monoxide (DLco) < 50% predicted
- Cardiac T2* < 10 ms by magnetic resonance imaging or other evidence of severe iron overload

The age of study participants ranged from 12 to 35 years. Thirteen participants had non-β0/β0 genotypes and 9 had β0/β0 genotypes. At a median follow-up of 26 months (range, 15 to 42 months), 12 of 13 participants with non-β0/β0 genotypes (βE/β0 or other) were free of transfusions. In the 9 participants with β0/β0 genotypes, the median annualized transfusion volume decreased by 73% and 3 participants were red-cell transfusion-independent. A total of 9 SAEs occurred, including 2 cases of veno-occlusive liver disease (grade 3 SAE) that were determined to be related to the busulfan conditioning. No replication-competent lentivirus was detected in any of the study participants.

Magrin and colleagues (2022) reported long-term outcomes in the 4 individuals from trial HGB-205, who were at least 5 years old. All 4 individuals remained transfusion-free though their last follow-up visit which occurred after 5.9, 4.9, 4.4 and 4.5 years, respectively. The total Hb at the last visit (g/L) in the 4 individuals were 105, 129, 82 and 113, respectively. No additional treatment-related SAEs were reported. Follow-up data beyond 2 years have not been published for the 18 individuals who participated in trial HGB-204.

All of the available studies are single-arm trials; no data comparing gene therapy to HSCT are available.

There are a number of open questions regarding betibeglogene autotemcel therapy for beta thalassemia. Betibeglogene autotemcel has only been studied in a relatively small number of individuals. Moreover, the long-term durability of the gene therapy remains unknown, with follow-up beyond 2 years only published for 4 individuals in the Phase I/II study (and longest follow up out to 4 years, as reported by the manufacturer). While the magnitude of treatment effect induced by betibeglogene autotemcel appears sufficient to result in a clinically meaningful level of transfusion independence in most treated individuals, it does not appear that treatment of individuals with beta thalassemia restores them to a healthy, non-diseased phenotype. In the phase III trial, nearly all individuals underwent iron chelation after treatment betibeglogene autotemcel infusion. Many treated individuals may need to restart iron reducing therapy given ongoing ineffective erythropoiesis. Four out of 36 (11%) individuals cited in the FDA approval did not achieve transfusion independence, presumably because of insufficient transduction of long-term hematopoietic stem cells being the likely cause. Further study is required to establish optimal transduction strategies.

Moreover, the safety of gene therapy for beta thalassemia has not been clearly established; most individuals in the phase III trial experienced SAEs such as thrombocytopenia or neutropenia. In addition, a clinical trial using a similar technology with a lentiviral vector for treatment of sickle cell disease was suspended for several months in 2021 due to 2 participants developing acute myeloid leukemia/myelodysplastic syndrome (AML/MDS). The investigative team found that busulfan was the likely cause of AML in 1 participant, but busulfan was excluded as the cause in the second participant. In addition to transplant conditioning regimens, hypotheses for the mechanism of leukemogenesis include insertional mutagenesis and expansion of preexisting premalignant clonal populations driven by regeneration of hematopoiesis with expansion of the autologous HSC population (Jones, 2021). Although cases of AML/MDS associated with gene therapy for beta thalassemia have not been identified, with the small number of individuals studied, such an adverse event cannot be ruled out.

A 2021 expert opinion guideline on transfusion-dependent thalassemia from the Thalassemia International Federation (TIF) stated the following:

> Although waiting for the long-term clinical data on gene therapy for β-thalassemia, currently and on the basis of existing indications, patients with β-thalassemia major have potentially the following options for treatment:

- allogeneic hematopoietic stem cell (HSC) transplantation: young patients (≤17-year-old) with a β+ or β0 genotype having an HLA-compatible sibling or a 10/10 matched volunteer donor.
- gene therapy with Zynteglo: young patients in the 12- to 17-year-old age group with a β+genotype who do not have an HLA-compatible sibling donor.
- gene therapy with Zynteglo: patients in the 17- to 55-year-old age group with a β+genotype who do not have severe comorbidities and are at-risk or ineligible to undergo an allo-HSC transplant but can otherwise undergo an autologous gene therapy procedure with an acceptable risk.

The FDA approval announcement includes cautionary text addressing concerns of risk of insertional oncogenesis, stating the following:

There is a potential risk of LVV mediated insertional oncogenesis after treatment with ZYNTEGLO. Patients treated with ZYNTEGLO may develop hematologic malignancies and should be monitored lifelong. Monitor for hematologic malignancies with a complete blood count (with differential) at Month 6 and Month 12 and then at least annually for at least 15 years after treatment with ZYNTEGLO, and integration site analysis at Months 6, 12, and as warranted.

In summary, available data supports betibeglogene autotemcel for treatment of individuals with transfusion-dependent beta thalassemia who are candidates for an allogeneic hematopoietic cell transplantation, but lack a suitable donor, when serious concomitant illness is not present, including evidence of severe iron overload. While the therapy is considered potentially curative, long-term data on both safety and effectiveness is lacking (the longest follow-up in studies is 4 years). Over ten percent of participants enrolled in Zynteglo clinical trials failed to achieve independence from blood transfusion, likely because an insufficient number of stem cells were modified by gene therapy. As well, nearly half of treated individuals needed to restart iron removal therapy, presumably because of ongoing ineffective development of red blood cells. As with other gene therapies, long-term safety remains unknown, including a potential risk of blood cancer.

Gene Editing

It should be noted that in some of the published clinical trial reports, exagamglogene autotemcel is referred to as exa-cel or CTX001.

Exagamglogene autotemcel (Casgevy™) was approved by the FDA on January 16, 2024, for the treatment of individuals aged 12 and older with transfusion-dependent beta thalassemia (TDT). This product had previously been approved by the FDA for treatment of sickle cell disease with recurrent vaso-occlusive crises. The product was approved for single intravenous administration only.

FDA approval was based on data from 52 individuals who participated in the CLIMB THAL-111 trial. Data were not published in a peer-reviewed journal at the time of FDA approval; however, they were subsequently published by Locatelli and colleagues in 2024. A total of 35 of 52 participants were included in the primary efficacy analysis. The efficacy data set included 11 adolescents between 12 and 18 years old and 24 individuals between 18 and 35 years old.

Key inclusion criteria of the CLIMB THAL-111 trial (NCT03655678) were:

- Individuals 12 years to 35 years of age.
- Diagnosis of TDT as defined by:
  - Documented homozygous β-thalassemia or compound heterozygous β-thalassemia including β-thalassemia/hemoglobin E (HbE).
  - History of at least 100 mL/kg/year or ≥ 10 units/year of packed red blood cell (RBC) transfusions in the prior 2 years before signing the consent or the last rescreening for patients going through re-screening.
- Eligible for autologous stem cell transplant as per investigator's judgment.

Key exclusion criteria for the CLIMB THAL-111 trial included the following:

- A willing and healthy 10/10 HLA-matched related donor available per investigator's judgement.
- Prior allogeneic HSCT.
- Subjects with associated α-thalassemia and more than one alpha deletion or alpha multiplications.
- Subjects with sickle cell β-thalassemia variant.
- Clinically significant and active bacterial, viral, fungal, or parasitic infection as determined by the investigator.
- White blood cell (WBC) count < 3×10^9/L or platelet count < 50×10^9/L not related to hypersplenism.

The median follow-up for the analysis reported in Locatelli (2024) was 20.4 months (minimum of 2.1 months and maximum of 48.1 months) from the time of Casgevy infusion. None of the individuals experienced graft failure or graft rejection.

The primary outcome of the analysis was the proportion of treated individuals achieving transfusion independence for 12 consecutive months. This was defined as maintaining a weighted average of Hb ≥ 9 g/dL without red blood cell transfusions for at least 12 consecutive months during the 2 years after Casgevy infusion. In the analysis, 32 of 35 (91.4%, 95% CI, 77% to 98%) treated individuals met criteria for the primary outcome. All of the individuals who achieved transfusion independence maintained it for the remainder of the analysis period; there was a mean duration of transfusion independence of 22.5 months (range, 13.3 to 45.1 months). Among the 3 individuals who did not achieve transfusion independence, 1 had a relative reduction from baseline of 85% in the annualized red blood-cell transfusion volume. The other 2 individuals stopped red-cell transfusions at 14.5 months and 12.2 months after Casgevy infusion and were transfusion-free for 7.3 months and 4.0 months, respectively, starting 60 days after the final infusion.

All of the 52 study participants experienced at least one adverse event after Casgevy infusion; most of these were grade 1 or 2 in severity. A total of 46 individuals (88%) had grade 3 or 4 adverse events. There were 17 individuals (33%) with serious adverse events, the most common of which was veno-occlusive disease in 5 participants. The most common adverse events of any severity were febrile neutropenia in 28 individuals (54%), stomatitis in 21 individuals (40%), anemia in 20 individuals (38%), a platelet count decrease in 18 individuals (35%) and thrombocytopenia in 18 individuals (38%).

Another published study was a case series with 2 individuals treated with Casgevy, 1 with sickle cell disease and 1 with beta thalassemia (Frangoul, 2021). Eligibility was limited to people who were between the ages of 18 and 35 years. Individuals with beta thalassemia with either homozygous or compound heterozygous gene variants were eligible if they had received transfusions of packed red cells consisting of at least 100 ml per kilogram of body weight (or 10 units) per year during the previous 2 years. Individuals with sickle cell disease 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 HL)-matched related donor, and prior allogeneic hematopoietic stem cell transplantation.

After undergoing exa-cel preparation and myeloablation, each participant 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 3% to 93% of total hemoglobin in the beta thalassemia participant; from 9% to 43% in the sickle cell disease participant), transfusion independence, and (in the participant with sickle cell disease) elimination of vaso-occlusive episodes. The clinical course of both participants was similar to the phenotype of hereditary persistence of HbF levels. Adverse events were reported in both individuals 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 summary, available data supports exagamglogene autotemcel for treatment of individuals with transfusion-dependent beta thalassemia who are candidates for an allogeneic hematopoietic cell transplantation, but lack a suitable donor, when serious concomitant illness is not present, including evidence of severe iron overload. While the therapy is considered potentially curative, the product has been studied in a small number of individuals and only data from an interim analysis of a single clinical trial are available. Nearly ten percent of participants in the Casgevy trial interim analysis failed to achieve independence from blood transfusion, likely because an insufficient number of stem cells were modified by gene therapy. Moreover, long-term data on effectiveness is lacking. In addition, the safety of gene therapy for beta thalassemia has not been clearly established; all of the 52 individuals studied reported adverse events, most had serious adverse events. As with other gene therapies, long-term safety remains unknown, including a potential risk of blood cancer.

Background/Overview

The thalassemias are a group of inherited blood disorders that reduce the production of hemoglobin in the blood. When individuals do not have enough hemoglobin, their red blood cells, which carry oxygen to cells throughout the body, do not develop normally and this causes anemia (shortage of red blood cells) and other health problems such as fatigue, weakness, as well as an increased risk of developing blood clots.

Normal hemoglobin has four protein sub-units, two of which are alpha globin and two of which are beta globin. Abnormalities in the genes that produce alpha globin cause alpha thalassemia and abnormalities in the genes that produce beta globin cause beta thalassemia. For beta thalassemia, the relevant gene is the human beta-globin (HBB) gene. Some mutations in the HBB gene prevent all production of beta-globin; the complete absence of beta-globin is called beta zero (β0) thalassemia. Other mutations in the HBB gene allow a reduced amount of beta-globin to be produced; this condition is known as beta-plus (β+) thalassemia. The presence of either β0 or β+ thalassemia does not necessarily predict the severity of disease. Coinheritance of the genetic variant βE (HBB:c.79G→A) with any β0 mutation results in a βE/β0 genotype, a condition of varying severity that is responsible for approximately half of all cases of transfusion-dependent β-thalassemia worldwide.

Beta thalassemia is inherited in an autosomal recessive manner. That is, more severe disease occurs in individuals who inherit an altered copy of the genes from both parents. Individuals with both genes altered can have either beta thalassemia intermedia which causes moderate anemia or severe beta thalassemia, known as thalassemia major or Cooley’s anemia. Individuals with one altered copy of the gene and one normal copy, known as beta thalassemia minor or beta thalassemia carrier, are generally asymptomatic or have mild symptoms.

In affected individuals, signs and symptoms of beta thalassemia occur between 6 and 24 months of age (Origa, 2021). Children can present with failure to thrive (to gain weight or grow at the expected rate), jaundice or severe life-threatening

anemia. There may also be feeding problems, diarrhea, irritability, recurrent fevers and enlargement of the abdomen due to spleen or liver enlargement. If beta thalassemia is untreated or inadequately treated, the clinical effects include growth retardation, poor musculature, and skeletal changes including deformities of the long bones of the legs and characteristic facial changes.

If adequately treated so that individuals maintain a minimum hemoglobin concentration of 9.5 to 10.5 g/dl, growth and development are generally normal until about age 10 to 12 years but iron overload from regular transfusions can cause impeded growth and failure or delay of puberty. Long-term complications of treatment include heart disease, liver disease, enlargement of the spleen, endocrine disease such as diabetes, infections such as hepatitis B or C, venous thrombosis and osteoporosis (Origa, 2021; National Organization for Rare Disorders, 2018).

The annual incidence at birth of symptomatic beta thalassemia major is estimated at 1 in 100,000 worldwide. It is estimated that about 60,000 symptomatic individuals are born each year, the vast majority of whom are located outside of North America and Northern Europe (Ali, 2021).

Beta thalassemia anemia is diagnosed by blood tests such as analysis of hemoglobin by electrophoresis or high performance liquid chromatography (HPLC). Moreover, beta thalassemia is on the list of core newborn screening tests recommended by the U.S. government (Health Resources and Services Administration, 2020). Individual states, however, make the final decision on which tests to include in their newborn panels.

The primary treatment for beta thalassemia is blood transfusions. Individuals with beta thalassemia intermedia may need occasional blood transfusions when they experience symptoms or when they have an infection or other illness. Individuals with beta thalassemia major (also called transfusion-dependent beta thalassemia) require regular blood transfusions every 2 to 4 weeks. Repeated blood transfusions, however, can lead to a buildup of iron in the blood or iron overload. These individuals require chelation therapy to remove the excess iron. In addition, individuals are at increased risk of infection, which is a common cause of death in people with beta thalassemia.

Individuals with beta thalassemia major who do not receive regular blood transfusions and chelation therapy generally die before the 2nd or 3rd decade, and survival is higher in treated individuals. Cardiac complications remain the primary cause of morbidity and mortality in individuals with beta thalassemia. Due to the logistical difficulty and costs of treatments, many individuals do not comply with the recommended regimen of transfusions and chelation therapy and experience disease-related complications (Srivastava, 2017).

Allogeneic hematopoietic stem cell transplant (HSCT) has been available as a potentially curative treatment of beta thalassemia for several decades. This involves the transplantation of stem cells from the donor’s bone marrow or peripheral blood cells, and essentially involves replacing defective genes with healthy genes from another individual. Allogeneic HSCT is most effective when it is performed early in the course of disease before individuals experience complications related to transfusions or iron overload, ideally before 14 years of age. Survival rates of 90% or higher for early allogeneic HSCT have been reported. The decision to pursue HSCT is influenced by the availability of a well-matched donor; while the presence of human leukocyte antigen [HLA]-identical sibling donor is considered optimal, registry data has found similar survival outcomes in individuals who received HLA-matched related and HLA-matched unrelated donor transplantation (Li, 2019). Recent experiences evaluating transplantation with haploidentical donors in individuals with TDT have reported promising outcomes (Sun, 2018). HCT outcomes from the European Group for Blood and Marrow Transplantation registry database on 1493 individuals with beta thalassemia major transplanted after year 2000 found an overall survival for the whole cohort at two years of 88% (range 68 to 91%) (Baronciani, 2016). Potential complications of HSCT include graft rejection and GVHD (Srivastava, 2017).

Gene therapy, either viral vector gene therapy or gene editing therapy, is another potential curative treatment for beta thalassemia. Betibeglogene autotemcel (Zynteglo, Bluebird Bio) viral vector gene therapy involves inserting a functional copy of the HBB gene into a patient’s hematopoietic stem cells outside the body using a lentiviral vector and then transplanting the modified stem cells back into the patient’s blood stream, with the aim that the functional HBB gene will result in normal beta-globin protein expression. The use of autologous stem cells in gene replacement therapy removes the need for a compatible stem cell donor which has limited the ability of individuals to receive allogeneic SCT. Lentivirus vectors are used because they are capable of accepting the insertion and complex DNA sequences.

In August 2022, the FDA approved a one-time single-dose intravenous dose of Zynteglo for the following indication: “ZYNTEGLO is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell (RBC) transfusions.” No contraindications were listed.

The product label also describes the following procedures that are required prior to Zynteglo infusion:

Mobilization and Apheresis

- Patients are required to undergo HSC mobilization followed by apheresis to obtain CD34+ cells for product manufacturing.
- The target number of CD34+ cells to be collected is ≥ 12 × 10^6 CD34+ cells/kg. If the minimum dose of 5.0 × 10^6 CD34+ cells/kg is not met, the patient may undergo additional cycles of mobilization and apheresis, separated by at least 14 days, in order to obtain more cells for additional manufacture. Up to two drug product lots may be administered to meet the target dose.
- A back-up collection of CD34+ cells of ≥ 1.5 × 10^6 CD34+ cells/kg (if collected by apheresis) or > 1.0 × 10^8 TNC/kg (Total Nucleated Cells, if collected by bone marrow harvest) is required. These cells must be collected from the patient and be cryopreserved prior to myeloablative conditioning. The back-up collection may be needed for rescue treatment if there is: 1) compromise of hematopoietic stem cells or ZYNTEGLO before infusion, 2) primary engraftment failure, or 3) loss of engraftment after infusion with ZYNTEGLO.

Myeloablative Conditioning

- Full myeloablative conditioning must be administered before infusion of ZYNTEGLO. Consult prescribing information for the myeloablative conditioning agent(s) prior to treatment.
- Stop iron chelation at least 7 days prior to myeloablative conditioning. Prophylaxis for hepatic veno-occlusive disease (VOD) is recommended [see Clinical Studies (14)]. Prophylaxis for seizures should be considered, as appropriate.
- Do not begin myeloablative conditioning until the complete set of infusion bag(s) constituting the dose of ZYNTEGLO has been received and stored at the treatment center and the availability of the back-up collection is confirmed. After completion of the myeloablative conditioning, allow a minimum of 48 hours of washout before ZYNTEGLO infusion.

The gene editing therapy product, exagamglogene autotemcel (Casgevy) 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 the product, 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 Casgevy is prepared receive single-agent busulfan myeloablation before receiving the therapy in order to suppress the ability of bone marrow to produce native blood cells. The individuals are then infused with the autologous 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. There are examples of CRISPR-Cas9 gene editing resulting in genetic damage as a consequence of off-target editing (Kosicki, 2018).

In January 2024, exagamglogene autotemcel (Casgevy) was approved by the FDA for the treatment of individuals aged 12 and older with transfusion-dependent beta thalassemia. This product had previously been approved by the FDA for treatment of sickle cell disease with recurrent vaso-occlusive crises. The product was approved for single intravenous administration only. The product label notes that individuals are required to undergo HSC mobilization followed by apheresis to obtain CD34+cells for product manufacturing.

The product label for Casgevy included the following 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)

The product label also describes the following procedures that are required prior to Casgevy infusion:

- Preparation Before CASGEVY Infusion
  - Confirm that hematopoietic stem cell (HSC) transplantation is appropriate for the patient before mobilization, apheresis and myeloablative conditioning are initiated.
  - Screen patients for HIV-1, HIV-2, HBV, HCV, and any other infectious agents in accordance with local guidelines before collection of cells for manufacturing. CASGEVY should not be used in patients with active HIV-1, HIV-2, HBV or HCV.
  - Prior to apheresis procedure it is recommended that patients be transfused with a goal to maintain hemoglobin (Hb) ≥ 11 g/dL
- Mobilization and Apheresis
  - Patients are required to undergo CD34+ HSC mobilization followed by apheresis to isolate the CD34+ cells needed for CASGEVY manufacturing.
  - Plerixafor and Granulocyte-Colony Stimulating Factor (G-CSF) were used for mobilization in patients with TDT.
- Myeloablative Conditioning
  - In patients with TDT it is recommended that patients be transfused to maintain hemoglobin (Hb) ≥ 11 g/dL for 60 days prior to myeloablative conditioning.

Definitions

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

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.

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

Gene replacement 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.

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 betibeglogene autotemcel (Zynteglo) or exagamglogene autotemcel (Casgevy) 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 Zynteglo or Casgevy gene therapy product]

HCPCS

J3392	Injection, exagamglogene autotemcel, per treatment [Casgevy]
J3393	Injection, betibeglogene autotemcel, per treatment [Zynteglo]

ICD-10-PCS

XW133B8	Transfusion of betibeglogene autotemcel into peripheral vein, percutaneous approach, new technology group 8
XW143B8	Transfusion of betibeglogene autotemcel into central vein, percutaneous approach, new technology group 8
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 Zynteglo or Casgevy gene therapy:**
6A550ZV	Pheresis of hematopoietic stem cells, single
6A551ZV	Pheresis of hematopoietic stem cells, multiple

ICD-10 Diagnosis

D56.1	Beta thalassemia

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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Peer Reviewed Publications:

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Government Agency, Medical Society, and Other Authoritative Publications:

1. Farmakis D, Porter J, Taher A et al. Thalassaemia International Federation guidelines for the management of transfusion-dependent thalassemia. Hemasphere. 2022; 6(8):e732.
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Websites for Additional Information

1. U.S. National Library of Medicine Genetics Home Reference. Beta Thalassemia. Available at: https://medlineplus.gov/genetics/condition/beta-thalassemia/. Accessed on June 20, 2024.

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Beti-cel
Casgevy
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Exa-cel
Lentiglobin
Zynteglo

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 Rationale, References, and Website 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 J3393 replacing NOC codes for Zynteglo.
Revised	02/15/2024	MPTAC review. Added MN statement on exagamglogene autotemcel. Revised NMN statement. Updated Description/Scope, Rationale, Background/Overview, Definitions, References and Index sections. Updated Coding section, added ICD-10-PCS codes XW133J8, XW143J8.
Revised	01/16/2024	MPTAC review. Changed title to Gene Therapy for Beta Thalassemia. Revised MN statement. Removed INV&NMN statement on lovotibeglogene autotemcel. Updated Description/Scope, Rationale, Background/Overview and References sections. Updated Coding section to remove XW133H9, XW143H9 now addressed in MED.00146.
Revised	08/10/2023	MPTAC review. Changed title to Lentiviral Gene Therapy for Beta Thalassemia and Sickle Cell Disease. Added INV&NMN statement on lovotibeglogene autotemcel. Updated Description/Scope, Rationale, Background/Overview, Index sections. Updated Coding section with 10/01/2023 ICD-10-PCS changes to add XW133H9, XW143H9; also removed 30233C0; 30243C0 no longer applicable.

Revised	11/10/2022	MPTAC review. Removed umbilical cord blood and haploidentical donor from note to criterion B in medically necessary statement. Removed prior malignancy from criterion D in medically necessary statement. Description/Scope, Background/Overview and References sections updated.
New	08/19/2022	MPTAC review. Initial document development.
Preliminary Discussion	08/11/2022	MPTAC Pre-FDA approval review.

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.