MASSACHUSETTS

Blue Cross Blue Shield of Massachusetts is an Independent Licensee of the Blue Cross and Blue Shield Association

Medical Policy

# Gene Therapies for Thalassemia

## Table of Contents


- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References


## Policy Number: 215

BCBSA Reference Number: 5.01.42 (For Plan internal use only)
NCD/LCD: N/A

## Related Policies

Prior Authorization Request Form for Zynteglo® (Betibeglogene autotemcel), #216
Prior Authorization Request Form for Casgevy™ (Exagamglogene autotemcel) for Beta thalassemia, #217
Gene Therapies for Sickle Cell Disease, #050
Prior Authorization Request Form for Casgevy Gene Therapies for Sickle Cell Disease, #055

## Policy

### Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
### Medicare HMO Blue$^{SM}$ and Medicare PPO Blue$^{SM}$ Members

**Betibeglogene autotemcel (Zynteglo®)**

Zynteglo® (Betibeglogene autotemcel) is considered **MEDICALLY NECESSARY** and may be covered for individuals with transfusion-dependent β-thalassemia if the following criteria are met:

1. Documented diagnosis of β-thalassemia by globin gene testing; **AND**
2. Require regular peripheral blood transfusions to maintain target hemoglobin levels; **AND**
3. Documented history of receiving transfusions of ≥100 ml per kilogram of body weight of packed red cells per year or who had disease that had been managed under standard thalassemia guidelines with ≥8 transfusions per year in the previous 2 years at the time of treatment decision; **AND**
4. Karnofsky performance status of ≥80 for adults (≥16 years of age) or a Lansky performance status of ≥80 for adolescents (<16 years of age); **AND**
5. Negative serologic test for HIV infection (as per US FDA prescribing label, apheresis material from individuals with a positive test for HIV will not be accepted for Betibeglogene autotemcel manufacturing); **AND**
6. Individual does not have
    i. A provider-determined unacceptable risk-benefit with a willing and available human leukocyte antigen-identical or human leukocyte antigen-matched donor; **OR**

ii. T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec or other evidence of severe iron overload in the opinion of treating physician; **OR**
iii. Advanced liver disease (meets any one of the following):
    a. Persistent aspartate transaminase, alanine transaminase, or direct bilirubin value greater than 3 times the upper limit of normal; **OR**
    b. Baseline prothrombin time or partial thromboplastin time greater than 1.5 times the upper limit of normal; **OR**
    c. Magnetic resonance imaging of the liver demonstrating clear evidence of cirrhosis; **OR**
    d. Liver biopsy demonstrating cirrhosis, any evidence of bridging fibrosis, or active hepatitis; **OR**
iv. Baseline estimated glomerular filtration rate less than 70 mL/min/1.73 $m^2$; **OR**
v. History of receiving prior gene therapy or allogenic hematopoietic stem cell transplant; **OR**
vi. Any prior or current malignancy (with the exception of adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin) or myeloproliferative or significant immunodeficiency disorder; **OR**
vii. Any immediate family member (i.e. parent or siblings) with a known Familial Cancer Syndrome (including but not limited to hereditary breast and ovarian cancer syndrome, hereditary nonpolyposis colorectal cancer syndrome and familial adenomatous polyposis); **OR**
viii. Active, uncontrolled HCV or HBV infection; **OR**
ix. Contraindication to the use of granulocyte colony stimulating factor (G-CSF), plerixafor, busulfan, or any other medicinal products required during myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients; **OR**
x. A white blood cell count less than 3 X $10^9$/L, and/or platelet count less than 100 X $10^9$/L not related to hypersplenism.

Betibeglogene autotemcel is considered **INVESTIGATIONAL** when the above criteria are not met.

Repeat treatment of betibeglogene autotemcel is considered **INVESTIGATIONAL.**

Betibeglogene autotemcel is considered **INVESTIGATIONAL** for all other indications.

**Exagamglogene autotemcel (Casgevy®)**

Exagamglogene autotemcel are considered **MEDICALLY NECESSARY** for individuals with transfusion-dependent β-thalassemia if they meet criteria 1 through 6:

1. Documented diagnosis of β-thalassemia (e.g., β-thalassemia major and thalassemia intermedia) by globin gene testing.
2. Require regular peripheral blood transfusions to maintain target hemoglobin levels as defined by the following:
    i. History of receiving transfusions of ≥100 mL per kilogram of body weight of packed red blood cells per year OR
    ii. History of receiving ≥8 transfusions per year in the previous 2 years at the time of treatment decision.
3. Meet the institutional requirements for a stem cell transplant procedure where the individual is expected to receive gene therapy. These requirements may include:
    i. Adequate Karnofsky performance status or Lansky performance status
    ii. Absence of advanced liver disease
    iii. Adequate estimated glomerular filtration rate (eGFR)
    iv. Adequate left ventricular ejection fraction (LVEF)
    v. Absence of clinically significant active infection(s).
4. Have not had a T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec or other evidence of severe iron overload in the opinion of treating physician.
5. Have not received a previous allogenic hematopoietic stem cell transplant.

6. Do not have a current application pending for another gene therapy for beta thalassemia.

Exagamglogene autotemcel are considered **INVESTIGATIONAL** when the above criteria are not met.

Exagamglogene autotemcel is considered **INVESTIGATIONAL** for all other indications except sickle cell disease. (Coverage information of Exagamglogene autotemcel for sickle cell disease is addressed in medical policy #050.)

Repeat treatment with Exagamglogene autotemcel is considered **INVESTIGATIONAL**.

## Policy Guidelines

**Recommended Dose:**

**Betibeglogene autotemcel**
Betibeglogene autotemcel: minimum dose is 5.0 $\times 10^6$ CD34+ cells/kg of body weight.

**Exagamglogene autotemcel**
Exagamglogene autotemcel: minimum dose is 3.0 $\times 10^6$ CD34+ cells/kg of body weight.

**Dosing Limits:** 1 injection per lifetime

**Other considerations**
Drug-drug interactions between iron chelators and the myeloablative conditioning agent must be considered. Iron chelators should be discontinued at least 7 days prior to initiation of conditioning. Some iron chelators are myelosuppressive. It is recommended to avoid use of non-myelosuppressive iron chelators for at least 3 months and use of myelosuppressive iron chelators for at least 6 months after the infusion of exagamglogene autotemcel or lovotibeglogene autotemcel. Phlebotomy can be used in lieu of iron chelation, when appropriate.
Per the Food and Drug Administration (FDA) prescribing label, neither product has been studied in patients > 65 years of age.

Betibeglogene autotemcel only: there is a potential risk of lentiviral vector-mediated insertional oncogenesis after treatment. It is recommended that individuals be monitored for hematological malignancies at month 6, month 12, and then annually at least 15 years after treatment with betibeglogene autotemcel.

## Prior Authorization Information

**Inpatient**

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

**Outpatient**

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

| | Outpatient |
|---|---|
| **Commercial Managed Care (HMO and POS)** | Prior authorization is **required*** |
| **Commercial PPO and Indemnity** | Prior authorization is **required*** |
| **Medicare HMO Blue℠** | Prior authorization is **required*** |
| **Medicare PPO Blue℠** | Prior authorization is **required*** |

Prior Authorization Request Form: Zynteglo™ (Betibeglogene autotemcel) for Beta thalassemia, #216
Prior Authorization Request Form: Casgevy™ (Exagamglogene autotemcel) for Beta thalassemia, #217
*The form must be completed and faxed to: Medical and Surgical: 1-888-282-0780;
Medicare Advantage: 1-800-447-2994.

**Requesting Prior Authorization Using Authorization Manager**
Providers will need to use Authorization Manager to submit initial authorization requests for services. Authorization Manager, available 24/7, is the quickest way to review authorization requirements, request authorizations, submit

clinical documentation, check existing case status, and view/print the decision letter. For commercial members, the requests must meet medical policy guidelines.

To ensure the request is processed accurately and quickly:
- Enter the facility's NPI or provider ID for where services are being performed.
- Enter the appropriate surgeon's NPI or provider ID as the servicing provider, *not* the billing group.

**Authorization Manager Resources**
- Refer to our Authorization Manager page for tips, guides, and video demonstrations.

**For out of network providers:** Requests should still be faxed to 888-973-0726.

## CPT Codes / HCPCS Codes / ICD Codes

*Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.*

*Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.*

*The following codes are included below for informational purposes only; this is not an all-inclusive list.*

**The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

### HCPCS Codes

| HCPCS codes | Code Description |
|---|---|
| C9399 | Unclassified drugs or biologicals |
| J3392 | Injection, exagamglogene autotemcel, per treatment (Casgevy®) |
| J3393 | Injection, betibeglogene autotemcel, per treatment (Zynteglo®) |
| J3490 | Unclassified drugs |
| J3590 | Unclassified biologics |

### ICD-10 Procedure Codes

| ICD-10 PCS Procedure Codes | Code Description |
|---|---|
| XW133B8 | Transfusion of Betibeglogene Autotemcel into Peripheral Vein, Percutaneous Approach, New Technology Group 8 |
| XW133J8 | Transfusion of Exagamglogene Autotemcel into Peripheral Vein, Percutaneous Approach, New Technology Group 8 |
| XW143B8 | Transfusion of Betibeglogene Autotemcel into Central Vein, Percutaneous Approach, New Technology Group 8 |
| XW143J8 | Transfusion of Exagamglogene Autotemcel into Central Vein, Percutaneous Approach, New Technology Group 8 |

## Summary

β-Thalassemia

It is an inherited blood disorder that occurs as a result of a genetic variant in the HBB gene that codes for the production of β-globin chains. As a result, there is reduced synthesis or absence of β-globin chains leading to impaired production of hemoglobin. The clinical presentation is that of anemia which requires iron supplementation and multiple downstream sequelae from the disease. These sequelae include growth retardation, skeletal changes (particularly in the face and long bones of the legs), osteoporosis, leg ulcers, and development of extramedullary masses. High

output heart failure from anemia is also common without treatment. Without transfusion therapy, such patients die within the first few years of life, primarily from heart failure or infection.

Life expectancy of individuals with transfusion-dependent β-thalassemia is much lower than population norms. From 2011 to 2021 the median age of death for a person in the US with transfusion-dependent β- thalassemia was 37.2, Additionally, individuals with transfusion-dependent β-thalassemia report decreased quality of life due to the impact on physical and mental health.

All humans have 2 copies of the HBB gene, and each copy produces the β-globin protein. Different types of β-thalassemia categorized by genotype are summarized in Table 1. When only 1 HBB gene is affected, the phenotype is less severe, and individuals are generally asymptomatic due to compensation from the other normal gene. These individuals are called β-thalassemia minor or carrier. However, if both copies of HBB gene are affected there is a quantitative reduction or absence of β-globin protein. Phenotypes that manifest as a reduction in β-globin chains are referred to as "β-thalassemia intermedia" and phenotypes that manifest as absence in β-globin chains are called "β-thalassemia major".

More recently, patients have been classified according to their transfusion status (i.e., transfusion-dependent β-thalassemia or non-transfusion-dependent β-thalassemia). For this evidence review, we will focus on transfusion-dependent β-thalassemia patients which generally includes "β-thalassemia major" but occasionally may include patients with "β-thalassemia intermedia". Clinical studies reviewed define "transfusion dependence" as history of at least 100 mL/kg/year of peripheral red blood cells or ≥8 transfusions of peripheral red blood cells per year for the prior 2 years. "Transfusion independence" was defined as a weighted average hemoglobin (Hb) of at least 9 g/dL without any transfusions for a continuous period of at least 12 months at any time during the study after infusion of betibeglogene autotemcel.

**Table 1. Different Types of β-Thalassemia[5,6,7,]**

| Type | Genotype | Description |
|---|---|---|
| β-thalassemia major (generally transfusion dependent) | $\beta^0/\beta^0$ or $\beta^0/\beta^+$ | • Presents within the first 2 years of life with severe microcytic anemia (typical hemoglobin 3 to 4 g/dL), mild jaundice, and hepatosplenomegaly |
| | | • Requires regular red blood cell transfusions and other medical treatments |
| Thalassemia intermedia | $\beta^+/\beta^+$ | • Presents at a later age with similar, but milder, clinical signs and symptoms of thalassemia<br>• Moderately severe anemia; some may need regular blood transfusion |
| Thalassemia minor | $\beta/\beta^0$ or $\beta/\beta^+$ | • Also called "β-thalassemia carrier" or "β-thalassemia trait"<br>• Usually clinically asymptomatic but may have a mild anemia<br>• Generally do not require any treatment |

$\beta^0$ refers to no beta globin production; $\beta^+$ refers to decreased beta globin production

**Epidemiology**

β-thalassemia is one of the most common monogenic disorders, but its incidence varies geographically. Higher incidence and prevalence have been reported among individuals from Mediterranean, Africa, the Middle East, and Southeast Asia. While its occurrence is rare in United States, the pattern shows an increasing trend with migration and is expected to increase in the

future. According to Bluebird Bio, approximately 1500 people in the United States currently live with transfusion-dependent β-thalassemia.[8,]

**Diagnosis**

The diagnostic pathway for symptomatic thalassemia syndromes (thalassemia major and thalassemia intermedia) in a neonate, infant, or child begins with either recognition of symptoms (anemia, evidence of hemolysis and extramedullary hematopoiesis such as jaundice, skeletal abnormalities, and/or splenomegaly) or may be suspected based on a known family history. Initial laboratory testing includes a complete blood count, review of the blood smear, and iron studies. DNA-based genotyping of globin gene can be done relatively inexpensively, is required for precise diagnosis, and is especially important in carrier detection, prenatal testing, and genetic counseling.[5,]

**Treatment**

The current standard of care for transfusion-dependent β-thalassemia includes blood transfusion, iron chelation therapies, and allogenic hematopoietic stem cell transplant.

As per the 2014 Thalassemia International Federation guidelines, transfusion is indicated when hemoglobin levels are less than 7 g/dL on 2 different occasions more than 2 weeks apart, or when hemoglobin levels are greater than 7 g/dL but there are co-occurring complications such as facial changes, poor growth, fractures, or clinically significant extramedullary hematopoiesis. The goal of treatment is to maintain a hemoglobin level of 9 to 10.5 g/dL, which has been shown to promote normal growth, suppress bone marrow activity, and minimize iron accumulation.[9,10,] Transfusions are typically required every 2 to 5 weeks to reach this goal but can vary for patients such as those with heart failure who may require higher target hemoglobin levels.[11,] Risks of repeated blood transfusions include transfusion reactions, allergic reactions, hemolytic anemia, transfusion-related acute lung injury, and transfusion-related graft versus host disease and alloimmunization.[12,] In the event of alloimmunization, it becomes difficult to find a matched blood and also increases the likelihood of delayed transfusion reactions. However, the main complication from frequent blood transfusions is iron overload.

Iron overload as a result of frequent transfusion results in iron accumulation in the heart, liver, and pituitary gland and can lead to heart failure, cirrhosis, hepatocellular carcinoma, hypothyroidism, hypoparathyroidism, hypogonadism, diabetes, and growth failure.[13,] Primary treatment for iron overload is chelation therapy (desferrioxamine, deferasirox, deferiprone) and is typically initiated after 10 to 20 transfusions or when the serum ferritin level rises above 1000 mcg/L.[14,] Chelation therapy is associated with side effects such as hearing problems, bone growth retardation and local reactions, gastrointestinal symptoms, arthralgia, and neutropenia. Another limitation of chelation therapy is lack of adherence when infused therapies are used as compared to higher adherence for patients taking oral therapy.[15,]

Hematopoietic stem cell transplant is the only curative treatment with cure rates ranging from 80% to 90% in children who receive human leukocyte antigen-identical sibling transplant.[16,] Cure rates in adults are lower with a reported range of 65% to 70%.[17,] While the cure rates are high, the main limiting factor for hematopoietic stem cell transplant is lack of a compatible donor. Fewer than 25% of patients have compatible related or unrelated donors, and transplants with mismatched donors or unrelated umbilical cord blood have a lower success rate.[18,] Complications from hematopoietic stem cell transplant include mucositis, infection, graft failure, and graft versus host disease. If available, hematopoietic stem cell transplant should be offered to patients early in the disease course, prior to the onset of iron overload.[14,]

There are no randomized trials comparing hematopoietic stem cell transplant with medical therapy for transfusion-dependent thalassemia.[19,] Only a 2017 retrospective case-control study has been published, showing no statistically different overall survival with transplantation versus conventional medical therapy (eg, transfusions and iron chelation).[17,] The Center for International Blood and Marrow Transplant Research reported the results of a retrospective cohort of 1110 individuals with

β-thalassemia who received a hematopoietic stem cell transplant between 2000 and 2016. The median age at transplantation was 6 years (range: 1 to 25 years), 61% received transplants with grafts from HLA-matched related donors, 7% from HLA-mismatched related donors, 23% from HLA-matched unrelated donors, and 9% from HLA-mismatched unrelated donors. The results are summarized in Table 2.

**Table 2. Outcomes of Retrospective Cohort of Individuals Who Received Hematopoietic Stem Cell Transplant for β-Thalassemia**

| Outcome | Matched Sibling | Matched Unrelated | Mismatched Relative | Mismatched Unrelated |
|---|---|---|---|---|
| 5-year survival | 89% (n=677) | 87% (n=252) | 73% (n=78) | 83% (n=103) |
| Graft failure | 8.6% (n=677) | 5.2% (n=252) | 21.8% (n=78) | 10.7% (n=103) |
| Grade 2-4 acute GVHD | 11.9% (n=674) | 21.5% (n=251) | 35.1% (n=77) | 19.8% (n=101) |
| Chronic GVHD | 8.3% (n=627) | 8.4% (n=249) | 20% (n=70) | 23.8% (n=101) |

[a] Matched relative representative of matched sibling in this study.
GVHD: graft-versus-host disease.

**Betibeglogene autotemcel**

In the early phase of clinical development, 2 proof of concept studies HGB-205 (NCT02151526) and HGB-204 (NCT01745120) were conducted.[20,21,] The clinical response in these studies was less than expected. Subsequently, improvements in manufacturing process were made to enhance transduction to increase vector copy number and bolster clinical response. As such, these proof of concept studies were not included in the evidence review. The clinical development program of betibeglogene autotemcel for individuals with transfusion dependent β-thalassemia consists of 2 open-label, phase III, single-arm studies (HGB-207 and -212) that included a total of 41 study participants who received a single intravenous infusion of betibeglogene autotemcel. Of the 2 phase III studies, 1 has been published.[22,] Of the 41 participants, 36 participants in whom transfusion independence was evaluable were included in the efficacy analysis. Transfusion independence was achieved in 89% (95% confidence interval [CI], 74% to 97%) of study participants. The median duration of transfusion independence was not reached at the time of data cut-off.

**Summary of Evidence**

For individuals with transfusion-dependent β-thalassemia who receive betibeglogene autotemcel, the evidence includes 2 single-arm studies: HGB-207 (Northstar-2) and HGB-212 (Northstar-3). The Northstar-2 trial enrolled non- β0β0 genotype (less severe phenotype) while Northstar-3 trial enrolled β- thalassemia patients with either a β0or β+ IVS1 110 (G>A) variant (severe phenotype) at both alleles of the HBB gene. Relevant outcomes are change in disease status, quality of life, hospitalizations, medication use, treatment-related morbidity and treatment-related mortality. The 2 open-label, phase III, single-arm studies included a total of 41 individuals who received a single intravenous infusion of betibeglogene autotemcel. Of the 41 participants, 36 participants in whom transfusion independence was evaluable were included in the efficacy analysis. Transfusion independence was achieved in 89% (95% CI, 74% to 97%) of study participants. Limitations include a small sample size and limited duration of follow-up. There is uncertainty regarding the durability of effect over a longer time period. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect. The small sample size creates uncertainty around the estimates of some of the patient-important outcomes, particularly adverse events. Some serious harms are likely rare occurrences and, as such, may not be observed in small trials. While most of the serious adverse events were attributable to known risks associated with myeloablative conditioning, uncertainty still remains about the degree of risk with betibeglogene autotemcel infusion in real-world practice. Insertional oncogenesis has been identified as a potential risk with transgene integration. There has been no evidence of insertional oncogenesis and no malignancies in the trials of betibeglogene autotemcel. However, cases of myelodysplastic syndrome and acute myeloid leukemia have been reported in gene therapy trials that use a lentiviral vector to treat other conditions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

**Exagamglogene autotemcel**
The clinical development program of exagamglogene autotemcel for individuals with transfusion dependent β-thalassemia consists of one single-arm, open-label, phase 1/2/3 study called study 111 (NCT03655678) and the long-term follow-up study 131 (NCT04208529). The Food and Drug Administration (FDA) approval was based on the interim analysis with a cutoff date of January 16, 2023. In Study 111, 52 participants were dosed with exagamglogene autotemcel at the time of this analysis, of whom 35 participants had an adequate duration of follow-up (at least 16 months following exagamglogene autotemcel and at least 14 months since last RBC transfusion post-transplant) for evaluation of efficacy. Transfusion independence was achieved in 91% (32/35) (98.3% CI, 75.7% to 100%) of study participants. The median (range) transfusion free duration in the 32 participants was 20.8 (13.3, 45.1) months; no participant resumed transfusions after achievement of transfusion independence.

**Summary of Evidence**
For individuals with transfusion-dependent β-thalassemia who receive betibeglogene autotemcel, the evidence includes 2 single-arm studies: HGB-207 (Northstar-2) and HGB-212 (Northstar-3). The Northstar-2 trial enrolled non-$\beta^0\beta^0$ genotype (less severe phenotype) while Northstar-3 trial enrolled β-thalassemia patients with either a $\beta^0$or $\beta^+$ IVS1 110 (G>A) variant (severe phenotype) at both alleles of the *HBB* gene. Relevant outcomes are change in disease status, quality of life, hospitalizations, medication use, treatment-related morbidity and treatment-related mortality. The 2 open-label, phase III, single-arm studies included a total of 41 individuals who received a single intravenous infusion of betibeglogene autotemcel. Of the 41 participants, 36 participants in whom transfusion independence was evaluable were included in the efficacy analysis. Transfusion independence was achieved in 89% (95% confidence interval, 74% to 97%) of study participants. There is uncertainty regarding the durability of effect over a longer time period. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect. Limited sample size creates uncertainty around the estimates of some of the patient-important outcomes, particularly adverse events. Some serious harms are likely rare occurrences and, as such, may not be observed in trials. While most of the serious adverse events were attributable to known risks associated with myeloablative conditioning, uncertainty still remains about the degree of risk with betibeglogene autotemcel infusion in real-world practice. Insertional oncogenesis has been identified as a potential risk with transgene integration. There has been no evidence of insertional oncogenesis and no malignancies in the trials of betibeglogene autotemcel. However, cases of myelodysplastic syndrome and acute myeloid leukemia have been reported in gene therapy trials that use a lentiviral vector to treat other conditions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with transfusion-dependent β-thalassemia who receive exagamglogene autotemcel, the evidence includes 1 single-arm study: Study 111. This study enrolled patients with homozygous β-thalassemia or compound heterozygous β-thalassemia including β-thalassemia/hemoglobin E. Relevant outcomes are change in disease status, quality of life, hospitalizations, medication use, treatment-related morbidity and treatment-related mortality. The single open-label study included a total of 52 individuals who received a single intravenous infusion of exagamglogene autotemcel. Of the 52 participants, 35 participants in whom transfusion independence was evaluable were included in the interim efficacy analysis. Transfusion independence was achieved in 91% (98.3% confidence interval, 75.7% to 100%) of study participants. There is uncertainty regarding the durability of effect over a longer time period. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect. The limited sample size creates uncertainty around the estimates of some of the patient-important outcomes, particularly adverse events. Some serious harms are likely rare occurrences and as such may not be observed in trials. While most of the serious adverse events were attributable to known risks associated with myeloablative conditioning, uncertainty still remains about the degree of risk of exagamglogene autotemcel infusion in real-world practice. While no cases of malignancies or unintended, off-target genome editing were reported in the trial participants, off-target editing in an individual's CD34+ cells cannot be ruled out due to genetic variants especially in the larger, real-world, population. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

## Policy History

| Date | Action |
|---|---|
| 1/2025 | Clarified coding information |
| 8/2024 | Policy revised to include medically necessary and investigational indications for Exagamglogene autotemcel (Casgevy) for individuals with transfusion dependent beta thalassemia when certain conditions are met. Clarified coding information. Effective 8/1/2024. |
| 7/1/2024 | Clarified coding information. |

| | |
|---|---|
| 10/13/2022 | Policy created with literature review through August 17, 2022. The use of Betibeglogene autotemcel (Zynteglo) is considered medically necessary for individuals with transfusion dependent beta thalassemia when certain conditions are met. Effective 10/13/2022. |

## Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

## References


1. Borgna-Pignatti C. The life of patients with thalassemia major. Haematologica. Mar 2010; 95(3): 345-8. PMID 20207838
2. Chieco P and Butler C. 2021 CAF Information - The Cooleys Anemia Foundation. Published January 21st, 2022; Available at www.thalassemia.org/2021-caf-information/. Accessed January 21, 2024.
3. Arian M, Mirmohammadkhani M, Ghorbani R, et al. Health-related quality of life (HRQoL) in beta-thalassemia major (β-TM) patients assessed by 36-item short form health survey (SF-36): a meta-analysis. Qual Life Res. Feb 2019; 28(2): 321-334. PMID 30194626
4. Vitrano A, Calvaruso G, Lai E, et al. The era of comparable life expectancy between thalassaemia major and intermedia: Is it time to revisit the major-intermedia dichotomy?. Br J Haematol. Jan 2017; 176(1): 124-130. PMID 27748513
5. Langer AL. Beta-Thalassemia. 2000 Sep 28 [Updated 2023 Jul 20]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1426/
6. Galanello R, Origa R. Beta-thalassemia. Orphanet J Rare Dis. May 21 2010; 5: 11. PMID 20492708
7. Chonat S, Quinn CT. Current Standards of Care and Long Term Outcomes for Thalassemia and Sickle Cell Disease. Adv Exp Med Biol. 2017; 1013: 59-87. PMID 29127677
8. beta-thalassemia (beta-thal). Bluebird Bio. https://www.bluebirdbio.com/our-focus/beta-thalassemia. Accessed January 21, 2024.
9. Farmakis D, Porter J, Taher A, et al. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassemia. Hemasphere. Aug 2022; 6(8): e732. PMID 35928543
10. Cazzola M, Borgna-Pignatti C, Locatelli F, et al. A moderate transfusion regimen may reduce iron loading in beta-thalassemia major without producing excessive expansion of erythropoiesis. Transfusion. Feb 1997; 37(2): 135-40. PMID 9051086
11. Cazzola M, Locatelli F, De Stefano P. Deferoxamine in thalassemia major. N Engl J Med. Jan 26 1995; 332(4): 271-2; author reply 272-3. PMID 7808503
12. Kremastinos DT, Farmakis D, Aessopos A, et al. Beta-thalassemia cardiomyopathy: history, present considerations, and future perspectives. Circ Heart Fail. May 2010; 3(3): 451-8. PMID 20484195
13. Thompson AA, Cunningham MJ, Singer ST, et al. Red cell alloimmunization in a diverse population of transfused patients with thalassaemia. Br J Haematol. Apr 2011; 153(1): 121-8. PMID 21323889
14. Olivieri NF, Liu PP, Sher GD, et al. Brief report: combined liver and heart transplantation for end-stage iron-induced organ failure in an adult with homozygous beta-thalassemia. N Engl J Med. Apr 21 1994; 330(16): 1125-7. PMID 8133854
15. Trachtenberg F, Vichinsky E, Haines D, et al. Iron chelation adherence to deferoxamine and deferasirox in thalassemia. Am J Hematol. May 2011; 86(5): 433-6. PMID 21523808
16. Baronciani D, Angelucci E, Potschger U, et al. Hemopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000-2010. Bone Marrow Transplant. Apr 2016; 51(4): 536-41. PMID 26752139
17. Caocci G, Orofino MG, Vacca A, et al. Long-term survival of beta thalassemia major patients treated with hematopoietic stem cell transplantation compared with survival with conventional treatment. Am J Hematol. Dec 2017; 92(12): 1303-1310. PMID 28850704

18. Angelucci E, Matthes-Martin S, Baronciani D, et al. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. Haematologica. May 2014; 99(5): 811-20. PMID 24790059
19. Sharma A, Jagannath VA, Puri L. Hematopoietic stem cell transplantation for people with β-thalassaemia. Cochrane Database Syst Rev. Apr 21 2021; 4(4): CD008708. PMID 33880750
20. Thompson AA, Walters MC, Kwiatkowski J, et al. Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia. N Engl J Med. Apr 19 2018; 378(16): 1479-1493. PMID 29669226
21. Magrin E, Semeraro M, Hebert N, et al. Long-term outcomes of lentiviral gene therapy for the β-hemoglobinopathies: the HGB-205 trial. Nat Med. Jan 2022; 28(1): 81-88. PMID 35075288
22. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene Autotemcel Gene Therapy for Non-β 0 /β 0 Genotype β-Thalassemia. N Engl J Med. Feb 03 2022; 386(5): 415-427. PMID 34891223
23. Prescribing Label: Zynteglo (betibeglogene autotemcel) suspension for intravenous infusion. Available at https://www.bluebirdbio.com/-/media/bluebirdbio/Corporate%20COM/Files/Zynteglo/ZYNTEGLO_prescribing_information.pdf. Accessed January 21, 2024.
24. Prescribing Label: Casgevy (exagamglogene autotemcel) suspension for intravenous infusion. Available at https://www.casgevyhcp.com/sites/default/files/uspi-ppi_exagamglogene_autotemcel.pdf. Accessed February 5, 2024.
25. Institute for Clinical and Evidence Review. Betibeglogene Autotemcel for Beta Thalassemia: Effectiveness and Value (Final Evidence Report July 19, 2022). Available at https://icer.org/beta-thalassemia-2022/. Accessed January 21, 2024.
26. Standards of Care Guidelines for Thalassemia- 2012. Published by Childrens Hospital & Research Center Oakland. Available at https://thalassemia.com/documents/SOCGuidelines2012.pdf. Accessed January 21, 2024.