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Betibeglogene autotemcel

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Betibeglogene autotemcel (Zynteglo®) **may be considered medically necessary** if **ALL** the following criteria are met:

1. Adult and pediatric patients ≤50 years of age) with transfusion dependent beta-thalassemia; AND
2. Documented history of transfusions evidenced by:
    a. 100 mL/kg/per year or more of packed red blood cells (pRBCs); OR
    b. 8 or more transfusions of packed red blood cells (pRBCs) per year in the preceding 1 year; AND
3. Negative serologic test for HIV infection; AND
4. Clinically stable and eligible to undergo hematopoietic stem cell (HSC) mobilization; AND
5. Individual does NOT have ANY of the following:
    a. White blood cell count less than 3 x 10^9/Liter and/or platelet count less than 100 x 10^9 not related to hypersplenism;
    b. History of prior gene therapy or allogenic hematopoietic stem cell transplant;
    c. Severe iron overload;
    d. Advanced liver disease;
    e. Prior or current malignancy, myeloproliferative disorder, or significant immunodeficiency.

Repeat treatment of Betibeglogene autotemcel (Zynteglo®) **is considered experimental, investigational, and/or unproven**.

Betibeglogene autotemcel (Zynteglo®) **is considered experimental, investigational, and/or unproven** for all other indications.

Policy Guidelines

None.

Description

Beta-thalassemia (β-thalassemia)
β-thalassemia 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. (1)

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 United States (U.S.) 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. (3, 4)

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". (5)

More recently, patients have been classified according to their transfusion status (i.e., transfusion-dependent β-thalassemia or non-transfusion-dependent β-thalassemia). This medical policy 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 100mL/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
B-thalassemia major (generally transfusion dependent)	β^0/β^0 or β^0/β^+	• 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	β^+/β^+	• Presents at a later age with similar, but milder clinical signs and symptoms of thalassemia • Moderately severe anemia; some may need regular blood transfusions

Thalassemia minor	β/β^0 or β/β^+	• Also called "β-thalassemia carrier" or "β-thalassemia trait" • Usually clinically asymptomatic but may have a mild anemia • Generally do not require any treatment

β^0 refers to no beta globin production; β^+ refers to decreased beta globin production.
g/dL: grams per deciliter

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 the Mediterranean, Africa, the Middle East, and Southeast Asia. While its occurrence is rare in U.S., 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 U.S. 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 (e.g., 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)
Grad 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)

GVHD: graft versus host disease.

Betibeglogene autotemcel (Zynteglo®)
Betibeglogene autotemcel (Zynteglo®) is the first cell-based gene therapy for the treatment of adult and pediatric patients with beta-thalassemia who require regular red blood cell transfusions. A one-time product administered as a single dose, Zynteglo is customized using the patient's own bone marrow stem cells that are genetically modified to produce functional beta-globin, a hemoglobin component.

Regulatory Status
On August 17, 2022, Zynteglo® (betibeglogene autotemcel) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell transfusions. (23) It was granted a rare pediatric disorder voucher, as well as receiving Priority Review, Fast Track, Breakthrough Therapy, and Orphan designations from the FDA.

Rationale

This medical policy was developed in October 2022 and is based on a search of literature from the PubMed database as well as the U.S. Food and Drug Administration (FDA) label as of October 5, 2022.

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Transfusion Dependent β-Thalassemia
Clinical Context and Therapy Purpose

The purpose of betibeglogene autotemcel is to provide a treatment option that is an improvement on existing therapies. Potential benefits of this one-time therapy may include the following:

- Obviates the need for repeated blood transfusion thereby eliminating its downstream consequences such as iron overload and alloimmunization.
- Reduced complexity of one-time treatment.
- Novel mechanism of action or approach may allow successful treatment of patients for whom other available treatments have failed.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with transfusion-dependent β-thalassemia.

Interventions
The therapy being considered is betibeglogene autotemcel. In this gene therapy protocol, hematopoietic stem cells are mobilized using granulocyte colony stimulating factor and plerixafor followed by apheresis to obtain a CD34+ cell-enriched population. These cells are then transduced *ex vivo* by BB305 lentiglobin viral vector which adds functional copies of β^{A-T87Q}-globin gene that encodes β-globin protein. Patients receive myeloablative conditioning with busulfan to deplete endogenous hematopoietic stem cells, enabling therapeutic repopulation of the individual bone marrow with hematopoietic stem cells containing the transgene. The treatment with betibeglogene autotemcel requires inpatient hospitalization. Betibeglogene autotemcel must be administered in a qualified treatment center (hospital setting) by a physician(s) with experience in hematopoietic stem cell transplantation and treatment of patients with β-thalassemia.

Comparators
The following strategies are currently being used to make decisions about management of transfusion-dependent β-thalassemia: blood transfusion, iron chelation therapies, activin A traps or activin A receptor IIA ligands such as luspatercept, and allogenic hematopoietic stem cell transplant.

Outcomes
The general outcomes of interest are change in disease status, quality of life, hospitalizations, medication use, treatment-related mortality, and treatment-related morbidity (Table 3). Follow up at 5 years is of interest to monitor outcomes.

Table 3. Health Outcome Measures Relevant to Transfusion-Dependent Thalassemia

Outcome	Measure (Units)	Thresholds for Improvement/Decline or Clinically Meaningful Difference

Change in disease status	• Change in iron levels (including serum ferritin, liver iron concentration, and myocardial iron deposition) • Change in Hb levels • Reduction in transfusion frequency • Independence from transfusion • Reduction in severity of clinical sequelae iron overload such as pulmonary hypertension, cardiovascular events (e.g., arrhythmia and congestive heart failure), liver disease, venous thromboembolism, bone pain, etc.	Independence from transfusion defined in clinical trials as "weighted average Hb ≥ 9 g/dL without RBC transfusions for ≥12 months."
Quality of life	• Quality of life (in trials, generic and age-appropriate measures for quality of life such as Pediatric Quality of Life Inventory for pediatric and adolescent patients and EuroQol-5D and Short Form-36 were used).	-
Hospitalizations	• Reduction in frequency or length of hospital admission • Reduction in frequency of ER visit	Not applicable
Medication use	• Reduction or avoidance of iron-chelating therapy	Not applicable
Treatment-related mortality	• Mortality	Not applicable
Treatment-related morbidity	• Serious adverse events • Adverse events leading to treatment discontinuation	Not applicable

ER: emergency room; Hb: hemoglobin; RBC: red blood cells

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.

- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Nonrandomized Studies

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 policyB. 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% CI, 74% to 97%) of study participants. The median duration of transfusion independence was not reached at the time of data cut-off.

Clinical Studies from the U.S. Food and Drug Administration Prescribing Information for Betibeglogene autotemcel (Zynteglo)(23)

The efficacy of Betibeglogene autotemcel (Zynteglo) was evaluated in 2 ongoing Phase 3 open-label, single-arm, 24-month, multicenter studies (Study 1 and Study 2) in 41 patients aged 4 to 34 years with β-thalassemia requiring regular transfusions. Following completion of the 24-month parent studies, patients were invited to enroll in an ongoing long-term safety and efficacy follow-up study for an additional 13 years (Study 3).

Patients were considered to be eligible for the Phase 3 studies if they had a history of transfusions of at least 100 mL/kg/year of packed red blood cells (pRBCs) or with 8 or more transfusions of pRBCs per year in the 2 years preceding enrollment. Patients who had severely elevated iron in the heart (i.e., patients with cardiac T2* less than 10 msec by magnetic resonance imaging [MRI]) or advanced liver disease were not accepted into the studies. MRI of the liver was performed on all patients. Patients older than 18 years with MRI results demonstrating liver iron content ≥ 15 mg/g underwent liver biopsy for further evaluation. Patients younger than 18 years with MRI results demonstrating liver iron content ≥ 15 mg/g were excluded from the studies unless a liver biopsy (at the discretion of the investigator) could provide additional data to confirm eligibility. Patients with a liver biopsy demonstrating bridging fibrosis, cirrhosis, or active hepatitis, were also excluded.

Mobilization and Apheresis

All patients were administered granulocyte-colony stimulating factor (G-CSF) and plerixafor to mobilize stem cells prior to the apheresis procedure. The planned dose of G-CSF was 10 µg/kg/day in patients with a spleen, and 5 µg/kg/day in patients without a spleen, given in the morning on Days 1 through 5 of mobilization. The planned dose of plerixafor was 0.24 mg/kg/day, given in the evening on Days 4 and 5 of mobilization. Apheresis generally occurred

on mobilization Day 5 and 6 and if a third day of collection was needed, plerixafor and G-CSF dosing was extended to Day 6. The dose of G-CSF was decreased by half if the white blood cell (WBC) count exceeded 100 × 109/L prior to the day of apheresis. Most patients collected the minimum number of CD34+ cells to manufacture Zynteglo with 1 cycle of mobilization and apheresis.

Pre-treatment Conditioning

All patients received full myeloablative conditioning with busulfan prior to treatment with Zynteglo. The planned dose of busulfan was 3.2 mg/kg/day for patients 18 years and older as a 3-hour IV infusion daily for 4 consecutive days with a recommended target AUC0-24h of 3800-4500 µM*min. The planned dose of busulfan was 0.8 mg/kg for patients younger than 18 years of age as a 2-hour IV infusion every 6 hours for a total of 16 doses with a recommended target of AUC0-6h of 950-1125 µM*min.

The busulfan prescribing information was used for information on the appropriate method for determination of patient weight-based dosing. Busulfan dose adjustments were made as needed based on pharmacokinetic monitoring. In the clinical studies after completion of the 4-day course of busulfan, a washout period of at least 48 hours was required before Zynteglo administration. Busulfan levels were measured 48 hours after final dose of busulfan for retrospective confirmation of adequate washout.

All patients received anti-seizure prophylaxis with agents other than phenytoin prior to initiating busulfan. Phenytoin was not used for anti-seizure prophylaxis because of its induction of cytochrome P450 and resultant increased clearance of busulfan.

Prophylaxis for hepatic veno-occlusive disease (VOD)/hepatic sinusoidal obstruction syndrome was required with ursodeoxycholic acid or defibrotide, per institutional guidelines.

Zynteglo Administration

All patients (N = 41) were administered Zynteglo with a median (min, max) dose of 9.4 (5.0, 42.1) × 106 CD34+ cells/kg as an intravenous infusion.

After Zynteglo Administration

G-CSF was not recommended for 21 days after Zynteglo infusion in Phase 3 studies. A total of 24% of patients (N = 10/41) received G-CSF within 21 days after Zynteglo infusion.

Neutrophil engraftment was reported on median (min, max) Day 26 (13, 39) after Zynteglo infusion.

As Zynteglo is an autologous therapy, long-term immunosuppressive agents were not required in clinical studies.

Study 1

Study 1 (NCT02906202) is an ongoing Phase 3 open-label, single-arm, 24-month study to evaluate the efficacy of Zynteglo in 23 patients with β-thalassemia requiring regular transfusions and with a non-β^0/β^0 genotype. Nineteen out of 23 patients have rolled over into a long-term follow-up study (Study 3, NCT02633943) after Month 24.

The median (min, max) duration of follow-up is 29.5 (13.0, 48.2) months. All patients remain alive at last follow-up. There were no cases of graft versus-host disease (GVHD), graft failure, or graft rejection in the clinical studies.

The benefit of Zynteglo was established based on achievement of transfusion independence (TI), defined as a weighted average Hb ≥ 9 g/dL without any pRBC transfusions for a continuous period of ≥ 12 months at any time during the study, after infusion of Zynteglo. Of 22 patients evaluable for TI, 20 (91%, 95% CI: 71, 99) achieved TI with a median (min, max) weighted average Hb during TI of 11.8 (9.7, 13.0) g/dL. All patients who achieved TI maintained TI, with a min, max duration of ongoing TI of 15.7+, 39.4+ months (N = 20) (Table 4). The median (min, max) time to last pRBC transfusion prior to TI was 0.9 (0.5, 2.4) months following Zynteglo infusion. For the patients who were evaluable for TI and did not achieve TI (N = 2), a reduction of 32% and 31% in transfusion volume requirements and a reduction of 30% and 26% in transfusion frequency were observed from 6 months post-drug product infusion to last follow-up compared to pre-enrollment requirements.

After Zynteglo infusion, patient iron removal therapy was managed at physician discretion. Thirteen of the 20 patients who achieved TI are not on chelation therapy as of last follow-up. Of these, 9 (9/13 = 69%) patients did not restart chelation. Four patients (4/13 = 31%) restarted and then stopped iron chelation with a median time from last iron chelation use to last follow-up of 22.7 (7.1, 23.4) months. Of the 20 patients who achieved TI, 7 patients (35%) received phlebotomy to remove iron.

Study 2
Study 2 (NCT03207009) is an ongoing Phase 3 open-label, single-arm, 24-month study to evaluate the efficacy of Zynteglo in 18 patients with β-thalassemia requiring regular transfusions and a β^0/β^0 or non-β^0/β^0 (IVS-I- 110/IVS-I-110 or IVS-I-110/ β^0) genotype. Ten out of 18 patients have rolled over into a long-term follow-up study (Study 3, NCT02633943) after Month 24.

The median (min, max) duration of follow-up is 24.6 (4.1, 35.5) months. All patients remain alive at last follow-up. There were no cases of GVHD, graft failure, or graft rejection in the clinical study.

The efficacy of Zynteglo was established based on achievement of transfusion independence (TI), which is defined as a weighted average Hb ≥ 9 g/dL without any pRBC transfusions for a continuous period of ≥ 12 months at any time during the study, after infusion of Zynteglo. Fourteen patients are evaluable for TI. Of these, 12/14 (86%, 95% CI: 57, 98) achieved TI with a median (min, max) weighted average Hb during TI of 10.20 (9.3, 13.7) g/dL. All patients who

achieved TI maintained TI, with a min, max duration of ongoing TI of 12.5+, 32.8+ months (N = 12) (Table 4). The median (min, max) time to last pRBC transfusion prior to TI was 0.8 (0.0, 1.9) months following Zynteglo infusion. For the patients who were evaluable for TI and did not achieve TI (N = 2), 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.

After Zynteglo infusion, patient iron removal therapy was managed at physician discretion. Seven of the 12 patients who achieved TI are not on chelation therapy as of last follow-up. Of these, three (3/7 = 43%) patients did not restart chelation. Four patients (4/7 = 57%) restarted and then stopped iron chelation with a median time from last iron chelation use to last follow-up of 7.2 (6.0, 21.4) months. Of the 12 patients who achieved TI, one (8%) received phlebotomy to remove iron.

Table 4. Efficacy and Pharmacodynamic Outcomes for Patients Treated with Zynteglo who Achieved Transfusion Independence

	Study 1[a] (N=23)	**Study 2[a] (N=18)**	**Overall Results[a] (N=41)**
Transfusion Independence (TI)[b] n/Nc (%) [95% CI]	 20/22 (91%) [77, 99]	 12/14 (86%) [57, 98]	 32/36 (89%) [74, 97]
Weighted Average Total Hb during TI (g/dL) n median (min, max)	 20 11.8 (9.7, 13.0)	 12 10.2 (9.3, 13.7)	 32 11.5 (9.3, 13.7)
Duration of TI (months)[d] n median (min, max)	 20 NR (15.7+, 39.4+)	 12 NR (12.5+, 32.8+)	 NR (12.5+, 39.4+)
HbA^{T87Q} (g/dL) at Month 6 n median (min, max)	 18 8.9 (5.2, 10.6)	 11 8.9 (3.8, 12.0)	 29 8.9 (3.8, 12.0)
HbA^{T87Q} (g/dL) at Month 24 n median (min, max)	 18 8.9 (5.0, 11.4)	 8 9.8 (7.9, 12.4)	 26 9.1 (5.0, 12.4)
Hb[e] (g/dL) at Month 6 n median (min, max)	 20 11.7 (9.3, 13.3)	 12 10.2 (8.8, 13.2)	 32 11.4 (8.8, 13.3)

Hb[e] (g/dL) at Month 24			
n	17	9	27
median	12.5	10.9	11.9
(min, max)	(9.5, 13.3)	(9.7, 14.0)	(9.5, 14.0)

[a] Includes duration of follow-up from Study 3.
[b] Transfusion independence (TI): a weighted average Hb ≥ 9 g/dL without any pRBC transfusions for a continuous period of ≥ 12 months at any time during the study after Zynteglo infusion.
[c] N represents the total number of patients evaluable for TI, defined as patients who have completed their parent study (i.e., Month 24), or achieved TI, or will not achieve TI in their parent study.
[d] Based on Kaplan-Meier.
[e] Hb levels are summarized for patients who do not have pRBC transfusions in the prior 60 days.
NR = Not reached. Hb = Total Hb.

Total Unsupported Hemoglobin Across Studies
All 32 patients in the Phase 3 studies who achieved TI with Zynteglo maintained TI. These patients exhibited durable normal or near-normal total hemoglobin levels with a median (min, max) unsupported total Hb of 11.4 (9.5, 14.8) g/dL at last follow-up.

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 β^0or 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.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J3393

*Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
09/15/2023	Reviewed. No changes.
03/01/2023	New medical document. Betibeglogene autotemcel (Zynteglo®) may be considered medically necessary if ALL the following criteria are met: adult and pediatric patients (≤50 years of age) with transfusion dependent beta-thalassemia; AND documented history of transfusions evidenced by: 100 mL/kg/year or more of packed red blood cells (pRBCs) OR; 8 or more transfusions of packed red blood cells (pRBCs) per year in the preceding 1 year; AND negative serologic test for HIV infection; AND clinically stable and eligible to undergo hematopoietic stem cell (HSC) mobilization; AND individual does NOT have ANY of the following: white blood cell count less than 3 x 109/Liter and/or platelet count less than 100 x 109 not related to hypersplenism; history of prior gene therapy or allogenic hematopoietic stem cell transplant; severe iron overload; advanced liver disease; prior or current malignancy, myeloproliferative disorder, or significant immunodeficiency. Repeat treatment of Betibeglogene autotemcel (Zynteglo®) is considered experimental, investigational, and/or unproven. Betibeglogene autotemcel (Zynteglo®) is considered experimental, investigational, and/or unproven for all other indications.