Policy Number	**RX501.166**
Policy Effective Date	**12/15/2025**

Gene Therapies for Thalassemia

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Related Policies (if applicable)
RX501.167: Gene Therapies for Sickle Cell Disease

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. 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 generally accepted standards of medical care. 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™) and exagamglogene autotemcel (Casgevy®) **may be 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).
2. Require regular peripheral blood transfusions to maintain target hemoglobin levels as defined by the following:
   a) History of receiving transfusions of ≥100 mL per kilogram of body weight of packed red blood cells per year; OR
   b) 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:
   a) Adequate Karnofsky performance status or Lansky performance status;
   b) Absence of advanced liver disease;
   c) Adequate left ventricular ejection fraction (LVEF);
   d) Absence of clinically significant active infection(s).
4. Do not have evidence of severe iron overload in the opinion of treating physician.
5. Have not received a previous allogenic hematopoietic stem cell transplant.
6. Have not received any gene therapy for beta thalassemia.

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

Repeat treatment with betibeglogene autotemcel (Zynteglo™) and exagamglogene autotemcel (Casgevy®) **is considered experimental, investigational and/or unproven**.

Policy Guidelines

Recommended Dose

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

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

Dosing Limits

1 injection per lifetime

Clinical Requirements for a Stem Cell Transplant

The requirement for eligibility for a stem cell transplant varied between the pivotal trial for betibeglogene autotemcel and exagamglogene autotemcel. These requirements are summarized below:

- Adequate cell counts defined as WBC < 3×10^9/L or platelets < 50 to 100 × 10^9/L
- Adequate hear function defined as LVEF < 45% or cardiac T2* < 10 ms
- Advanced liver disease defined as ALT > 3x ULN, AST > 3x ULN, direct bilirubin value > 2.5x to 3x ULN, PT INR > 1.5x ULN, history of cirrhosis or any evidence of bridging fibrosis, or active hepatitis on liver biopsy
- Adequate performance status defined as Karnofsky performance status > 60 (≥ 16 years of age) or Lansky performance status > 60 (< 16 years of age)
- Adequate kidney function defined as eGFR < 60 to 70 mL/min/1.73 m^2
- Abbreviation Key: ALT: alanine aminotransferase, ANC: absolute neutrophil count; DLCO: lung diffusion testing; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; PT INR: prothrombin time international normalized ratio; T2: transverse relaxation time; ULN: upper limit of normal; WBC: white blood cells.

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.

Description

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 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). For this medical policy, 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 (5-7)

Type	Genotype	Description
β-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.

Epidemiology

β-thalassemia is 1 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 the United States, the pattern shows an increasing trend with migration and is expected to increase in the future. According to Bluebird Bio, approximately 1300 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 allogeneic hematopoietic stem cell transplant.

As per the 2021 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 based on clinical criteria such as significant symptoms of anemia, poor growth or failure to thrive, complications from excessive intramedullary hematopoiesis (e.g., pathologic fractures, facial changes), or clinically significant extramedullary hematopoiesis, irrespective of hemoglobin level. (9) 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. (10, 11) 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. (12) 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. (13) 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. (14) Primary treatment for iron overload is chelation therapy (deferoxamine, deferasirox, deferiprone) and is typically initiated after 10 to 20 transfusions or when the serum ferritin level rises above 1000 mcg/L. (9) 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. (9)

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)
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.

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.

On December 8, 2023, exagamglogene autotemcel (Casgevy) was approved by the FDA for the treatment of sickle cell disease in patients 12 years or older and a history of vaso-occlusive events. On January 16, 2024, the FDA expanded the approved indication to include treatment of patients aged 12 years and older with transfusion-dependent β-thalassemia.

Rationale

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 1 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 or exagamglogene 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 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 and exagamglogene autotemcel. Both are intended to be one-time gene therapies. However, the mechanism of action is different.

- For betibeglogene autotemcel, 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 $\beta^{A\text{-}T87Q}$-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.
- Similar to betibeglogene autotemcel, 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 edited by CRISPR/Cas9-technology at the erythroid specific enhancer region of the BCL11A gene to reduce BCL11A expression in erythroid lineage cells. After infusion, the edited CD34+ cells engraft in the bone marrow and differentiate to erythroid lineage cells with reduced BCL11A expression. Reduced BCL11A expression results in an increase in γ-globin expression and fetal hemoglobin protein production in erythroid cells. Reactivation of fetal hemoglobin increases the total hemoglobin levels and has the potential to reduce or eliminate the need for RBC transfusions by decreasing the severity of the anemia.

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.

Betibeglogene autotemcel

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 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. Both phase III studies have been published. (22, 23) 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. Study characteristics, baseline characteristics and results are summarized in Tables 4 to 6.

Table 4. Summary of Key Nonrandomized Trials Characteristics

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
HGB-207 (Northstar-2) NCT02906202 (22)	Single-arm prospective	US, EU, UK, Thailand	2016-2022	• Non β^0/β^0 genotype • Age ≤50 years • Transfusion dependent β-thalassemia[a] • Clinically stable and eligible to undergo HSCT **Primary endpoint:** • Transfusion independence (weighted average Hb ≥ 9 g/dL without RBC transfusions for ≥ 12 months at any time during	Betibeglogene autotemcel (N=23)	Target: 2 years As of March 9, 2021: Median 29.5 months (range, 13.0 to 48.2)

				the study after gene therapy infusion)		
HGB-212 (Northstar-3) NCT03207009 (23)	Single-arm prospective	US, EU, UK	2017-2022	• β0/β0 genotype • β0/IVS1-110 genotype • IVS1-110/IVS1-110 genotype • Age ≤50 years old • Transfusion dependent β thalassemia • Clinically stable and eligible to undergo HSCT **Primary endpoint:** • Transfusion independence (weighted average Hb ≥ 9 g/dL without RBC transfusions for ≥ 12 months at any time during the study after gene therapy infusion)	Betibeglogene autotemcel (N=18)	Target: 2 years As of March 9, 2021: Median 24.6 months (range, 4.1 to 35.5)

[a] ≥ 100 mL/kg/year of RBCs or ≥ 8 peripheral RBC transfusions/year, for prior 2 years.
EU: European Union; Hb: hemoglobin; HSCT: hematopoietic stem cell transplant; RBC: red blood cell; UK: United Kingdom; US: United States.

Table 5. Summary of Baseline Demographics and Disease Characteristics in the Pivotal Trials

Characteristic (24)	HGB-207 (n=23)	HGB-212 (n=18)
Genotype	non-β^0/β^0	12 β^0/β^0; 6 non-β^0/β^0
Age, median (range), years	15 (4, 34)	13 (4, 33)
Male, n (%)	48%	56%
Race, n (%)		
Asian	57%	39%
White	35%	56%
Other/not reported	9%	6%

Baseline[a] transfusion volume (mL/kg/year), median (min, max)	208 (142, 274)	194 (75, 289)
Baseline[a] transfusion frequency (transfusions per year), median (min, max)	16 (12, 37)	17 (11, 40)
Lansky or Karnofsky Performance Score		
All patients, minimum score	≥80	≥90
Percentage of patients with score of 100	52%	56%
Cardiac T2* at baseline (msec), median (min, max)	37 (21, 57)	37 (15, 75)
Serum ferritin at baseline (pmol/L), median (min, max)	4439 (784, 22517)	3275 (1279, 8874)
Liver iron concentration at baseline (mg/g), median (min, max)	5.3 (1, 41)	3.6 (1.2, 13.2)

[a] Baseline annualized based on data 2 years prior to enrollment.

Table 6. Summary of Key Nonrandomized Trial Results

Study	Transfusion Independence	Weighted Average Hb During Transfusion Independence[b] (g/dL)	Observed Duration of Transfusion Independence in months (median)	Grade 3 or 4 Adverse Events in >10% of Participants, %
HGB-207 (Northstar-2) (24)	23	20	20	-
Betibeglogene autotemcel	91% (20/22); 95% CI: 77% to 99%	11.8 (range: 9.7 to 13.0)	Not reached (range: 15.7 to 39.4)	-
HGB-212 (Northstar-3) (24)	18[a]	12	12	-
Betibeglogene autotemcel	86% (12/14); 95% CI: 57% to 98%	10.2 (range: 9.3 to 13.7)	Not reached (range: 12.5 to 32.8)	-

Combined (HGB-207 and HGB-212) (24)	36	32	32	41
Betibeglogene autotemcel	89% (32/36); 95% CI: 74% to 97%	11.5 (range 9.3 to 13.7)	Not reached (range: 12.5 to 39.4)	Neutropenia: 100% Thrombocytopenia: 100% Leukopenia: 100% Anemia: 95% Lymphopenia: 61% ALT Increased: 24% Hypophosphatemia: 20% Hyperglycemia: 14% Hypokalemia: 12% Hyperbilirubinemia: 10% Hyponatremia: 10%

ALT: alanine aminotransferase; CI: confidence interval; Hb: hemoglobin.

[a] 4 study participants were not evaluable for transfusion independence at the data cutoff of March 9, 2021

[b] The weighted average Hb is an average area under the curve during the period of transfusion independence, from the start of transfusion independence when the Hb is first >= 9 g/dL with no transfusions in the preceding 60 days to the last available Hb at which the transfusion independence criteria are still met.

The purpose of the study limitations tables (see Tables 7) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement. In addition to a limited sample, the length of follow-up is not long enough to remove uncertainty regarding the durability of effect over a longer time period. To date, no study participants that became transfusion independent have reverted to becoming transfusion dependent. Study participants in the phase III studies have a median duration of follow-up between 24 and 29 months. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect as well as side effects. No deaths were reported in any of the studies, but both mild side effects and serious adverse events were observed in the studies. The limited sample sizes of the studies create 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.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Combined (HGB-207 and HGB-212) (24)	4. Enrolled populations do not reflect relevant diversity.				1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Section Summary: Betibeglogene autotemcel

In the 2 pivotal, open-label, phase III single-arm studies, a total of 41 study participants 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. 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 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.

Exagamglogene autotemcel

Nonrandomized Studies

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. Study characteristics, baseline characteristics and results are summarized in Tables 8 to 10.

Table 8. Summary of Key Nonrandomized Trial Characteristics

Study	Study 111 (NCT03655678) (25, 26)
Study Type	Single-arm prospective
Country	United States, Europe, and United Kingdom
Dates	2018-Ongoing
Participants	Inclusion • Documented homozygous β-thalassemia or compound heterozygous β-thalassemia including β-thalassemia/hemoglobin E • History of ≥100 mL/kg/year or ≥10 units/year of RBC transfusions in the previous 2 years • Aged 12 to 35 years • Eligible for autologous HSCT Exclusion • Available 10/10 human leukocyte antigen-matched donor • Prior HSCT • Sickle cell β-thalassemia variant or associated α-thalassemia and >1 alpha deletion or alpha multiplications • WBC count <$3x10^9$/L or platelet count <$50x10^9$/L not related to hypersplenism • Severely elevated iron in the heart (cardiac T2* less than 10 msec by MRI or LVEF <45% by echocardiogram) or advanced liver disease[a] **Primary endpoint:** • Transfusion independence (weighted average Hb ≥ 9 g/dL without RBC transfusions for ≥ 12 months at any time within the first 24 months after gene therapy infusion)
Treatment	Exagamglogene autotemcel (N=52)
Follow-Up	Target: 2 years

	As of January 2023: Median follow-up 23.8 months (range, 16.1 to 48.1 months)

[a] Advanced liver disease defined as aspartate transaminase or alanine transaminase >3x the upper limit of normal, or direct bilirubin value >2.5x the upper limit of normal, or if a liver biopsy demonstrated bridging fibrosis or cirrhosis (liver biopsy was performed if liver iron content was ≥15 mg/g by MRI)
Hb: hemoglobin; HSCT: hematopoietic stem cell transplant; RBC: red blood cell; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; WBC: white blood cells.

Table 9. Summary of Baseline Demographics and Disease Characteristics in the Pivotal Trial

Characteristic	**Study 111 (n=35) (25)**
Age, median (range), years	20 (12, 33)
Adults (≥ 18 and ≤ 35 years), %	68.6%
Adolescents (≥ 12 and < 18 years), %	31.4%
Male, n (%)	51.4%
Race, n (%)	
Asian	37.1%
White	42.9%
Multiracial	8.6%
Genotype	
β^0/β^0-like[a]	57.1%
Non-β^0/β^0-like[a]	42.9%
Baseline transfusion volume (mL/kg/year), median (min, max)	205 (115, 331)
Baseline transfusion frequency (transfusions per year), median (min, max)	17 (11, 35)
Cardiac T2* at baseline (msec), median (min, max)	34.8 (19.6, 61.1)
Serum ferritin at baseline (pmol/L), median (min, max)	2654 (674, 10741)
Liver Iron concentration at baseline (mg/g), median (min, max)	4.0 (1.4, 14.0)

[a] Low to no endogenous β-globin production (β^0/β^0, β^0/IVS-I-110 and IVS-I-110/IVS-I-110)

Table 10. Summary of Key Nonrandomized Trial Results

Study	Study 111 (25)
Transfusion Independence	91.4% (32/35); 98.3% CI: 75.7% to 100%
Weighted Average Hb During Transfusion Independence, mean (SD) (g/dL)	13.1 (±1.4)
Observed Duration of Transfusion Independence in months, median (range)	20.8 (13.3, 45.1)
Grade 3 or 4 Adverse Events in >10% of Participants, %	Febrile neutropenia: 54% Mucositis: 71%

	Veno-occlusive liver disease: 10% Decreased appetite: 23% Epistaxis: 13%

CI: confidence interval; Hb: hemoglobin; SD: standard deviation

The purpose of the study limitations tables (see Table 11) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement. In addition to a limited sample, the length of follow-up is not long enough to remove uncertainty regarding the durability of effect over a longer time period. To date, no study participants that became transfusion independent have reverted to becoming transfusion dependent. Study participants in the pivotal study have a median duration of follow-up of 23 months. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect as well as side effects. No deaths were reported in any of the studies, but both mild side effects and serious adverse events were observed in the studies. Limited sample size of the study 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 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.

Table 11. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Study 111 (25)					1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Section Summary: Exagamglogene autotemcel

In the pivotal, open-label, single-arm study, a total of 52 study participants 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% CI, 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.

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^0 or 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% 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.

Practice Guidelines and Position Statements

Institute for Clinical and Economic Review

The Institute for Clinical and Economic Review published a final report on comparative effectiveness and value of betibeglogene autotemcel for beta thalassemia on July 19, 2022. (27) The Report concluded that betibeglogene autotemcel to be incremental or better with moderate certainty of a small or substantial net health benefit ("B+") versus standard of care.

National Institute for Health and Care Excellence (NICE)

On September 11, 2024, the NICE issued technology appraisal guidance on exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia in people 12 years and over. (28) Exagamglogene autotemcel is recommended with managed access as an option for treating transfusion-dependent beta-thalassaemia in people 12 years and over:

- When a HSCT is suitable, but a human leukocyte antigen-matched related hematopoietic stem cell donor is not available.
- Only if the conditions in the managed access agreement for exa-cel are followed.

Cooley's Anemia Foundation

The Children's Hospital & Research Center Oakland published the standards of care guidelines for thalassemia in 2012. (29) These guidelines have not been updated since they were published.

Ongoing and Unpublished Clinical Trials

Ongoing and unpublished trials that might influence this policy are listed in Table 12.

Table 12. Summary of Ongoing and Unpublished Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Betibeglogene autotemcel			
NCT02633943[a]	Long-term Follow-up of Subjects With Transfusion-Dependent β-Thalassemia Treated With Ex Vivo Gene Therapy	66	Nov 2035
Exagamglogene autotemcel			
NCT05477563	Evaluation of Efficacy and Safety of a Single Dose of CTX001 in Participants With Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease	26	Feb 2025
NCT05356195	Evaluation of Safety and Efficacy of CTX001 in Pediatric Participants With Transfusion-Dependent β-Thalassemia	15	May 2026
NCT04208529	A Long-term Follow-up Study in Participants Who Received CTX001	160	Sep 2039
NCT03655678	A Safety and Efficacy Study Evaluating CTX001 in Subjects With Transfusion-Dependent β-Thalassemia	59	Dec 2025

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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	J3392, J3393

*Current Procedural Terminology (CPT®) ©2024 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 <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
12/15/2025	Document updated with literature review. Medical document combined with RX501.148 Betibeglogene autotemcel. Along with the addition of language specific to betibeglogene autotemcel, the following changes were made to Coverage: 1) Revised medically necessary criteria for both betibeglogene autotemcel and exagamglogene autotemcel; and 2) Added “non-Food and Drug Administration approved” to the experimental, investigational and/or unproven statement. Added references 9, 20-24, and 26-29. Title changed from “Exagamglogene autotemcel”.
03/15/2025	Reviewed. No changes.
05/01/2024	New medical document. Exagamglogene autotemcel (Casgevy™) may be considered medically necessary for the treatment of sickle cell disease in individuals 12 years of age or older with and a history of vaso-occlusive events when all the criteria listed in Coverage are met. Exagamglogene autotemcel (Casgevy™) may be considered medically necessary for the treatment of transfusion-dependent β-thalassemia in individuals 12 years of age and older and a documented history of transfusions when all the criteria listed in Coverage are met. Repeat treatment with exagamglogene autotemcel (Casgevy™) is considered experimental, investigational, and/or unproven. Exagamglogene autotemcel (Casgevy™) is considered experimental, investigational and/or unproven for all other indications.