Zynteglo (betibeglogne autotemcel)

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BENEFIT APPLICATION

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DESCRIPTION

The intent of the policy is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. The indications below including FDA-approved indications and compendial uses are considered covered benefits provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

Populations	Interventions	Comparators	Outcomes
Individuals: Who have transfusion-dependent β-thalassemia	**Interventions of interest are:** Betibeglogene autotemcel	**Comparators of interest are:** Standard of care	**Relevant outcomes include:** • Change is disease status • Quality of life • Hospitalizations • Medication use • Treatment-related morbidity • Treatment-related mortality

Beta-thalassemia

β-thalassemia is a genetic hemoglobinopathy that results from defects in β-globin synthesis leading to reduced synthesis or absence of β-globin chains causing impaired production of hemoglobin. The clinical presentation is that of anemia which requires transfusion and multiple downstream sequelae from iron overload. It is estimated that at least 1000 people in the United States have transfusion-dependent β-thalassemia. Betibeglogene autotemcel contains autologous CD34+ hematopoietic stem cells in which functional copies of a modified form of the β-globin gene (*βA-T87Q*-globin gene) have been added. Once the hematopoietic stem cells reengineered with $\beta^{A\text{-}T87Q}$ are infused, they engraft in the bone marrow and differentiate to produce red blood cells containing $\beta^{A\text{-}T87Q}$ gene that will produce HbA^{T87Q} protein (functional

gene therapy-derived hemoglobin) at levels that may eliminate or significantly reduce the need for transfusions.

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.

Additional Information

Not applicable.

Objective

The objective of this evidence review is to determine if use of betibeglogene autotemcel in individuals with transfusion-dependent β-thalassemia improves the net health outcome.

POLICY

Prior approval is required. Submit a prior approval/treatment request with required medical records and clinical documentation to (515) 376-9008.

Criteria for Initial Approval

Betibeglogene autotemcel is considered **medically necessary** for individuals with transfusion-dependent β-thalassemia if they meet criteria 1 through 6:

1. Documented diagnosis of β-thalassemia by globin gene testing.
2. Require regular peripheral blood transfusions to maintain target hemoglobin levels.
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.
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).

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).
6. Individual does not have:
    a. Availability of human leukocyte antigen-identical or human leukocyte antigen-matched donor.
    b. 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
    c. Advanced liver disease (meets any one of the following):
        i. Persistent aspartate transaminase, alanine transaminase, or direct bilirubin value greater than 3 times the upper limit of normal.
        ii. Baseline prothrombin time or partial thromboplastin time greater than 1.5 times the upper limit of normal.
        iii. Magnetic resonanceimagain of the liver demonstrating clear evidence of cirrhosis.
        iv. Liver biopsy demonstrating cirrhosis, any evidence of bridging fibrosis, or active hepatitis.
    d. Baseline estimated glomerular filtration rate less than 70 mL/min/1.73 m^2.
    e. History of receiving prior gene therapy or allogenic hematopoietic stem cell transplant.
    f. 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.
    g. 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).
    h. Active, uncontrolled HCV or HBV infection.
    i. 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.
    j. 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.

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

Continuation of Therapy

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

Dosing

The minimum recommended dose is 5.0 X 10^6 CD34+ cells/kg of body weight.

Quantity Limits

1 injection per lifetime

Other Considerations

- Prophylaxis for hepatic veno-occlusive disease is recommended. Prophylaxis for seizures should be considered.
- Monitor platelet counts until platelet engraftment and recovery are achieved. Individuals should be monitored for thrombocytopenia and bleeding.
- Monitor absolute neutrophil counts after betibeglogene autotemcel infusion. If neutrophil engraftment does not occur administer rescue cells.

- Monitor individuals at least annually for hematologic malignancies for at least 15 years after betibeglogene autotemcel infusion.
- Individuals should not take prophylactic anti-retroviral medications or hydroxyurea for at least 1 month prior to mobilization or the expected duration for elimination of the medications, and until all cycles of apheresis are completed as anti-retroviral medications may interfere with manufacturing of the apheresed cells.
- Iron chelators should be discontinued at least 7 days prior to initiation of conditioning. After betibeglogene autotemcel infusion, avoid use of these iron chelators for 6 months. If iron chelation is needed, consider administration of non-myelosuppressive iron chelators. Phlebotomy can be used in lieu of iron chelation, when appropriate.

BACKGROUND

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.[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 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.[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 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)	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 transfusion
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 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	Mismatached 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.

CLINICAL RATIONALE

This evidence review was created in August 2022 with a search of the PubMed database. The most recent literature update was performed through August 17, 2022.

Evidence reviews 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 he 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 review.

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 $\beta^{A\text{-}T87Q}$-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.

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 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 adolescents 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 cell.

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 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% 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 and results are summarized in Table 4 and 5.

Table 4. Summary of Key Nonrandomized Trials

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
HGB-207 (Northstar-2) NCT02906202[22,]	Single-arm prospective	United States, Europe, 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 the study after gene therapy infusion)	Betibeglogene autotemcel (N=23)	Target: 2 years As of March 9, 2021: Median 29.5 months (range 13.0 to 48.2)
HGB-212 (Northstar-3) NCT03207009]	Single-arm prospective	United States, Europe, 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.
Hb: hemoglobin; HSCT: hematopoietic stem cell transplant; RBC: red blood cell.

***Table 5*. Summary of Key Nonrandomized Trials**

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)[23,]	22	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)[23,]	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-207and HGB 212)[23,]	36	32	32	41
Betibeglogene autotemcel	89% (32/36); 95% CI: 74% to 97%	1.5 (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 6) 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 small 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 small sample sizes of the studies 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.

***Table 6.* Study Relevance Limitations**

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Combined (HGB-207and HGB 212)[23,]	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 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: Transfusion Dependent β-Thalassemia

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. 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 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.

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.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.[24,] 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.

Cooley's Anemia Foundation

The Children's Hospital & Research Center Oakland published the standards of care guidelines for thalassemia in 2012.[25,] These guidelines have not been updated since they were published.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Ongoing trials that might influence this review are listed in Table 7.

Table 7. **Summary of Ongoing and Unpublished Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02633943[a]	Long-term Follow-up of Subjects With Transfusion-Dependent β-Thalassemia Treated With Ex Vivo Gene Therapy	94	March 2031

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

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

Codes	Number	Description
CPT	N/A	
HCPCS	C9399	Unclassified drugs or biologicals (Currently no specific code)
ICD10 CM	D56.1	Beta-thalassemia
ICD10 PCS	XW133B8	Transfusion of Betibeglogene Autotemcel into Peripheral Vein, Percutaneous Approach, New Technology Group 8 (eff 10/01/2022)
	XW143B8	Transfusion of Betibeglogene Autoemcel into Central Vein, Percutaneous Approach, New Technology Group 8 (eff 10/01/2022)
Type of Service	Drugs/Biologicals	
Place of Service	Inpatient/Outpatient	

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POLICY HISTORY

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