

Embarc Benefit Protection Policy

POLICY: Hematology – Gene Therapy – Zynteglo Embarc Policy

- Zynteglo™ (betibeglogene autotemcel intravenous infusion – Bluebird Bio)

REVIEW DATE: 02/11/2026

OVERVIEW

Zynteglo, an autologous hematopoietic stem cell-based gene therapy, is indicated for the treatment of beta-thalassemia in adult and pediatric patients who require regular red blood cell (RBC) transfusions.¹ The efficacy and safety of Zynteglo in children < 4 years of age have not been established; no data are available in this population.

Zynteglo is given as a one-time (per lifetime) single dose which contains a minimum of 5.0×10^6 cluster of differentiation 34+ (CD34+) cells/kg of body weight.¹ Zynteglo is given as an intravenous infusion. The median dose of Zynteglo in the pivotal trials was 9.4×10^6 CD34+ cells/kg. The manufacturing time (which includes quality control) can take up to 6 months. Patients need to undergo mobilization and apheresis procedures, as well as myeloablative conditioning, prior to Zynteglo infusion.

Zynteglo is prepared from the patient's own hematopoietic stem cells, which are obtained via apheresis procedure(s).¹ Zynteglo is a β^{A-T87Q} -globin gene therapy comprised of autologous CD34+ cells, containing hematopoietic stem cells transduced with BB305 lentiviral vector (LVV) encoding β^{A-T87Q} -globin. Zynteglo adds functional copies of a modified form of the β -globin gene (β^{A-T87Q} -globin gene) into individual hematopoietic stem cells.

Disease Overview

The condition of beta-thalassemia is a group of recessively inherited blood disorders caused by β -globin gene mutations that either reflect a reduced (β^+) or relative lack (β^0) of production of functional β -globin.² The attenuated or lack of hemoglobin (Hb) results in chronic anemia of varying degrees of severity and insufficient delivery of oxygen to the body. Those with severe anemia may require lifelong RBC transfusions and regular iron chelation to prevent iron overload. The extremely low Hb levels can lead to many types of symptoms and health-related issues (e.g., dizziness, weakness, fatigue, increased cardiac effort, tachycardia, poor growth) or ineffective erythropoiesis (e.g., bone changes, massive splenomegaly). An estimated 3,000 patients in the US have beta-thalassemia and slightly less than one-half of the patients are dependent on RBC transfusions.

Clinical Efficacy

The efficacy of Zynteglo was evaluated in two ongoing, open-label, 2-year, single-arm, Phase III trials that involved patients ≤ 50 years of age with transfusion-dependent beta-thalassemia (NORTHSTAR-2 and NORTHSTAR-3) who received one dose of Zynteglo.^{1,3,4} All patients underwent mobilization of stem cells (with granulocyte colony-stimulating factor and Mozobil® [plerixafor subcutaneous injection]) and pre-treatment myeloablative conditioning with busulfan prior to treatment with Zynteglo. NORTHSTAR-2 (n = 23) involved patients who had a non- β^0/β^0 genotype. NORTHSTAR-3 (n = 18) involved patients who had a β^0/β^0 or non- β^0/β^0 genotype. In NORTHSTAR-2, 91% of patients obtained transfusion independence, the primary endpoint. Among the patients who obtained transfusion independence, the median weighted average Hb during transfusion independence was 11.8 g/dL.¹ In NORTHSTAR-3, transfusion independence was achieved by 86% of patients. Among the patients who obtained transfusion

independence, the median weighted average Hb during transfusion independence was 10.2 g/dL. The median time for the last RBC transfusion prior to transfusion independence after administration of Zynteglo was slightly under 1 month in both trials. In total, 29 patients from NORTHSTAR-2 and NORTHSTAR-3 enrolled in a long-term extension. Data suggest durable results regarding transfusion independence as these two studies have had follow-up for over 24 months.

Guidelines

The Thalassemia International Federation (TIF) guidelines for the management of transfusion-dependent thalassemia (TDT) [2025] address the use of gene therapies, including Zynteglo.⁵ TIF notes that allogeneic hematopoietic cell transplantation (HCT) has been the first therapeutic option for curing TDT. Substantial improvement in patient outcomes has been observed with HCT over recent years due to multiple factors, including improved conditioning regimens, improved prevention of graft-versus-host disease (GVHD), more effective antibacterial, antiviral, and antifungal treatment, and significant improvement in the medical care of TDT. However, more than 60% of patients do not have a suitable sibling donor; although HCT from a matched unrelated donor can also lead to successful results. TIF notes that HCT should be offered to patients with TDT at an early age, before complications due to iron overload develop. Gene therapy (including Zynteglo) may redefine the role of allogeneic transplantation. TIF notes that for patients ≥ 14 years of age who do not have an HLA-identical family donor, gene therapy is an optimal therapeutic option to allogeneic HCT. The main advantages of gene therapy are that a donor is not needed and there are no limitations or risks associated with donor availability/compatibility; absence/reduction of immune-mediated complications (e.g., no risk of GVHD or graft rejection); and lower toxicity (e.g., from the conditioning regimen). These advantages may allow more patients to access a curative treatment. However, there are potential risks with gene therapy, including insertional mutagenesis/insertional oncogenesis and DNA alterations (associated with genome editing). To date, there have been no cases of insertional oncogenesis reported in patients with TDT who were treated with Zynteglo.

POLICY STATEMENT

Prior Authorization is recommended for benefit coverage of Zynteglo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zynteglo as well as the specialized training required for administration of Zynteglo, approval requires Zynteglo to be prescribed by a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. The approval duration is 1 year to allow for an adequate timeframe to prepare and administer one dose of therapy. If claims history is available, verification is required for certain criteria, as noted by **[verification in claims history required]**. For dosing criteria, verification of the appropriate weight-based dosing is required by the Medical Director as noted by **[verification required]**. In the criteria for Zynteglo, as appropriate, the symbol (†) is noted next to the specified gender. In this context, the specified gender is defined as follows: females/males are defined as individuals with the biological traits of a woman/man, regardless of the individual's gender identity or gender expression. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation.

Documentation: Documentation is required for use of Zynteglo where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information. All documentation must include patient-specific identifying information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zynteglo is recommended in those who meet the following criteria:

FDA-Approved Indication

- 1. Transfusion-Dependent Beta-Thalassemia.** Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, and P):
 - A)** Patient is ≥ 4 years of age; AND
 - B)** Patient has not received a gene therapy for beta-thalassemia in the past **[verification in claims history required]**; AND
Note: If no claim for Zynteglo or Casgevy (exagamglogene autotemcel intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Zynteglo or Casgevy.
 - C)** According to the prescribing physician, a hematopoietic stem cell transplantation is appropriate for the patient; AND
 - D)** Patient meets ONE of the following (i or ii):
 - i.** Patient does not have a Human Leukocyte Antigen (HLA)-matched donor; OR
 - ii.** Patient has an HLA-matched donor, but the individual is not able or is not willing to donate; AND
 - E)** Patient has ONE of the following genotypes as confirmed by genetic testing (i or ii):
 - i.** Non- β^0/β^0 genotype **[documentation required]**; OR
Note: Examples include β^0/β^+ , β^E/β^0 , and β^+/ β^+ .
 - ii.** β^0/β^0 genotypes **[documentation required]**; AND
Note: Other examples include $\beta^0/\beta^{+(IVS-I-110)}$ and $\beta^{+(IVS-I-110)}/\beta^{+(IVS-I-110)}$.
 - F)** Patient is transfusion-dependent, as defined by meeting ONE of the following (i or ii):
 - i.** Receipt of transfusions of ≥ 100 mL of packed red cells per kg of body weight per year in the previous 2 years **[documentation required]**; OR
 - ii.** Receipt of transfusions eight or more times per year in the previous 2 years **[documentation required]**; AND
 - G)** Patient meets BOTH of the following (i and ii):
 - i.** Patient has been evaluated for the presence of severe iron overload **[documentation required]**; AND
 - ii.** Patient does not have evidence of severe iron overload; AND
Note: Examples include abnormal myocardial iron results (a T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec), high liver iron concentration (≥ 15 mg/g), liver biopsy results suggest abnormalities, or clinical evidence of organ damage (e.g., endocrine comorbidities).
 - H)** Patient does not currently have an active bacterial, viral, fungal, or parasitic infection; AND
 - I)** Patient does not have any of the following (i and ii):
 - i.** Prior or current malignancy, myeloproliferative disorder, or significant immunodeficiency disorder; AND
Note: This does not include adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin.
 - ii.** Advanced liver disease **[documentation required]**; AND
Note: Examples include alanine transaminase or aspartate transaminase greater than three times upper limit of normal, direct bilirubin value greater than three times upper limit of normal, active hepatitis, extensive bridging fibrosis, or cirrhosis.
 - J)** According to the prescribing physician, patient will have been discontinued from iron chelation therapy for at least 7 days prior to myeloablative conditioning; AND

Note: Examples of iron chelators used for this condition include deferoxamine injection, deferiprone tablets or solution, and deferasirox tablets.

- K)** According to the prescribing physician, patient meets ALL of the following (i, ii, iii, and iv):
- i.** Patient will undergo mobilization, apheresis, and myeloablative conditioning; AND
 - ii.** A granulocyte-colony stimulating factor product and a hematopoietic stem cell mobilizer will be utilized for mobilization; AND
Note: Filgrastim products are examples of a granulocyte-colony stimulating factor therapy and Mozobil (plerixafor subcutaneous injection) is an example of a hematopoietic stem cell mobilizer.
 - iii.** Busulfan will be used for myeloablative conditioning; AND
 - iv.** Total hemoglobin level is ≥ 11.0 g/dL at BOTH of the following timepoints (a and b):
 - a)** Prior to mobilization; AND
 - b)** Prior to myeloablative conditioning; AND
- L)** Patient screening is negative for ALL of the following (i, ii, iii, and iv):
- i.** Human immunodeficiency virus-1 and -2 **[documentation required]**; AND
 - ii.** Hepatitis B virus **[documentation required]**; AND
 - iii.** Hepatitis C virus **[documentation required]**; AND
 - iv.** Human T-lymphotropic virus-1 and -2 **[documentation required]**; AND
- M)** According to the prescribing physician, a patient of reproductive potential meets ONE of the following (i or ii):
- i.** A female† of reproductive potential meets BOTH of the following (a and b):
 - a)** A negative serum pregnancy test will be confirmed prior to the start of mobilization and re-confirmed prior to myeloablative conditioning; AND
 - b)** Patient will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Zynteglo; OR
 - ii.** A male† of reproductive potential will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Zynteglo; AND
- N)** The medication is prescribed by a hematologist or a stem cell transplant specialist physician; AND
- O)** Current patient body weight has been obtained within 30 days **[documentation required]**; AND
- P)** If criteria A through O are met, approve one dose of Zynteglo by intravenous infusion to provide a one-time (per lifetime) single dose which contains a minimum of 5.0×10^6 CD34+ cells/kg of body weight **[verification required]**.
- Note: A single dose of Zynteglo is composed of one or more infusion bag(s).

† Refer to the Policy Statement.

Dosing. The recommended dose of Zynteglo is one dose by intravenous infusion to provide a one-time (per lifetime) single dose which contains a minimum of 5.0×10^6 CD34+ cells/kg of body weight.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zynteglo is not recommended in the following situations:

1. Prior Hematopoietic Stem Cell Transplantation.

Note: The prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.

Zynteglo has not been studied in a patient who has received a prior allogeneic or autologous hematopoietic stem cell transplant. Treatment with Zynteglo is not recommended.

2. Prior Receipt of Gene Therapy.

Prior receipt of gene therapy was a reason for patient exclusion in the two pivotal trials.

3. Concurrent Use with Aqvesme™ (mitapivat tablets) or Reblozyl® (luspatercept-aamt subcutaneous injection).

Patients who had previously received gene therapy were excluded from the Aqvesme pivotal study involving patients with TDT.⁶ Reblozyl was not utilized with Zynteglo in the pivotal trials assessing Zynteglo in patients with transfusion-dependent beta-thalassemia.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria.

Criteria will be updated as new published data are available.

REFERENCES

1. Zynteglo™ intravenous infusion [prescribing information]. Somerville, MA: Bluebird Bio; August 2022.
2. Taher AT, Musallam KM, Cappellini MD, et al. β -thalassemias. *N Engl J Med*. 2021;384:727-743.
3. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene autotemcel gene therapy for non- β^0/β^0 genotype β -thalassemia. *N Engl J Med*. 2022;386:417-427.
4. Kwiatowski JL, Walters MC, Hongeng S, et al. Betibeglogene autotemcel gene therapy in patients with transfusion-dependent, severe genotype β -thalassaemia (HGB-212): a non-randomized, multicenter, single-arm, open-label, single-dose, phase 3 trial. *Lancet*. 2024;404(10468):2175-2186.
5. Taher AT, Farmakis D, Porter JB, Cappellini MD, Musallam KM, editors. Guidelines for the Management of Transfusion-Dependent β -Thalassaemia (TDT) [Internet]. 5th ed. Nicosia, Cyprus: Thalassaemia International Federation; 2025. PMID: 40367250.
6. Cappellini MD, Sheth S, Taher AT, et al. ENERGIZE-T: a global, Phase 3, double-blind, randomized, placebo-controlled study of mitapivat in adults with transfusion-dependent alpha- or beta-thalassemia (slides) Presented at: the 66th American Society of Hematology Annual Meeting and Exposition; San Diego, CA; December 7-10, 2024. Available at: https://www.agios.com/wp-content/uploads/2024/12/409_ASH24_Sun940amPT.pdf. Accessed on January 29, 2026.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	In the Policy Statement, wording was revised to emphasize that approval for Zynteglo is one-time (per lifetime) as a single dose. The approval duration was changed from 6 months to 1 year to allow an adequate timeframe to prepare and administer Zynteglo. The requirement of verification in claims history was revised to add the qualifier “if claims history is available”. The revised statement is as follows: If claims history is available, verification is required for certain criteria as noted by [verification in claims history required]. A sentence was added that for the Dosing criteria, verification of appropriate weight-based dosing is required by the Medical Director as noted by [verification required]. The following changes were made for Transfusion-Dependent Beta-Thalassemia (previously listed as “Beta-Thalassemia”): 1. The required patient upper age threshold was clarified to be < 51 years (previously listed as ≤ 50 years). 2. Regarding use of Zynteglo in the past, the criterion was changed due to the recent approval of Casgevy for this indication. It now states that the patient has not received “a gene therapy for beta-thalassemia” in the past instead of requiring that the patient has <u>not</u> received Zynteglo in the past. It was added that there should <u>not</u> be claims present for Casgevy and that if claims history is not available, the prescribing physician confirms that the patient has not previously received Casgevy (previously, this only addressed Zynteglo). In the Note, the following statement was deleted: verify through claims history that the patient has <u>not</u> previously received Zynteglo. 3. The reference to matched family donor was changed to remove “family”. 4. Regarding the confirmation that the patient has a specific genotype, the phrase “by DNA analysis” was changed to “by genetic testing”. 5. In the requirements that define a patient as transfusion-dependent, the phrases “preceding enrollment” and “before enrollment” were removed. 6. The requirement was removed that the patient has received or is planning to receive prophylaxis for hepatic veno-occlusive disease/hepatic sinusoidal obstruction syndrome before myeloablative conditioning with busulfan. 7. The requirement was removed that the patient who is ≥ 16 years of age has a Karnofsky performance status score of ≥ 80, as well as the requirement that a patient < 16 years of age has a Lansky performance status score of ≥ 80. 8. The requirements were removed that within 30 days before intended receipt of Zynteglo that the patient has a white blood cell count ≥ 3 x 10⁹/L and has a platelet count ≥ 100 x 10⁹/L. 9. A requirement was added that the patient does <u>not</u> have significant immunodeficiency disorder. 10. Documentation requirements were added to the requirement previously in the policy that the patient does <u>not</u> have advanced liver disease. Also, the examples of liver disease provided in the Note were revised. 11. The requirements were removed that the patient does <u>not</u> have the presence of any the following: familial cancer syndrome or a history of such in their immediate family; an estimated glomerular filtration rate < 70 mL/min/1.73 m²; an uncorrected bleeding disorder; and a diffusion capacity of carbon monoxide < 50% of predicted. 12. Regarding iron chelation therapy, the phrase “according to the prescribing physician” was added in reference to the requirement that the patient has been discontinued from this therapy for at least 7 days prior to myeloablative conditioning. Also, the requirement was removed that use of iron chelators will be avoided for 6 months after infusion of Zynteglo. 13. The phrase “according to the prescribing physician” was added regarding the following: that the patient will undergo mobilization, apheresis, and myeloablative conditioning; that for mobilization, a granulocyte-colony stimulating factor product and a hematopoietic stem cell mobilizer will be utilized; and that busulfan will be used for myeloablative conditioning.	03/20/2024

HISTORY (CONTINUED)

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	14. The word “total” was added in reference to the requirement that the hemoglobin level is ≥ 11.0 g/dL. The wording “prescribing physician confirms” was changed to “according to the prescribing physician”. 15. A requirement was added that the patient is negative for both hepatitis B virus and hepatitis C virus. 16. The requirement was removed that a negative serum pregnancy test be confirmed before Zynteglo administration. 17. Dosing was clarified with emphasis that Zynteglo is given as a “one-time (per lifetime) single dose.” Also, [documentation required] was replaced with [verification required].	03/20/2024
Selected Revision	Transfusion-Dependent Beta-Thalassemia: The upper age threshold (< 51 years of age) was removed; the lower age threshold remains: Patient is ≥ 4 years of age. In the Note for the criterion regarding evidence of severe iron overload, the threshold for high liver iron concentration, ≥ 15.5 mg/g, was changed to ≥ 15 mg/g to align with labeling.	09/25/2024
Early Annual Revision	Transfusion-Dependent Beta-Thalassemia: The word “cellular” was removed from the requirement regarding screening for certain viruses prior to collection of cells for manufacturing. The criterion regarding females/males of reproductive potential was clarified that this pertains only to a patient of reproductive potential.	02/05/2025
Selected Revision	Transfusion-Dependent Beta-Thalassemia: The qualifier “Prior to collection of cells for manufacturing” was removed from the requirement regarding screening for certain viruses and the word “Patient” was added. The new criterion now reads: “Patient screening is negative for ALL of the following...”.	04/23/2025
Annual Revision	Transfusion-Dependent Beta Thalassemia. A Note was added that a single dose of Zynteglo is composed of one or more infusion bag(s). Conditions Not Recommended for Approval, the condition “Concurrent Use with Reblozyl (luspatercept-aamt subcutaneous injection)” was revised to “Concurrent Use with Aqvesme (mitapivat tablets) or Reblozyl (luspatercept-aamt subcutaneous injection)”.	02/11/2026