Molina Clinical Policy
Zynteglo (betibeglogene autotemcel): Policy No. 420

Last Approval: 12/11/2024
Next Review Due By: October 2025

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

This policy addresses the use of Zynteglo gene therapy for the treatment of transfusion dependent beta thalassemia (TDT).

Thalassemia is a heterogeneous group of autosomal recessive genetic disorders characterized by decreased or absent synthesis of globin chains leading to anemia and microcytosis. Clinically, there are two major forms: α-thalassemia and β-thalassemia.

Beta (β) thalassemia is a hereditary anemia caused by mutations in the hemoglobin β-globin (HBB) gene, resulting in impaired β-globin chain production. When β-globin is markedly reduced or absent, it leads to ineffective production and increased destruction of red blood cells, manifesting in clinically significant anemia. Individuals with β-thalassemia minor have a mutation in one HBB gene, while individuals with the intermediate and major forms have mutations in both HBB genes:

Minor (trait or carrier)	Mild Microcytosis
Intermedia (non-transfusion-dependent)	Moderate Microcytosis
Major (transfusion-dependent)	Severe microcytosis with target cells (typical Hb 3 to 4 g/dL)

β+ mutations result in reduced (but not absent) synthesis of β-globin. The degree of reduction in β-globin resulting from β+ mutations range from severe to mild. β0 mutations are severe and there is no detectable β-globin production from that mutated allele ([1]Benz and Angelucci 2024).

The Thalassemia International Federation (TIF) guidelines (2021) classify β-thalassemia phenotypically into two main groups based on clinical severity and transfusion requirement regardless of the underlying genotype: transfusion-dependent thalassemia and non-transfusion dependent thalassemia (Cappellini et al. 2021).

Transfusion-dependent β-thalassemia (TDT; previously thalassemia major) is a rare, severe genetic disease characterized by reduced or absent production of the β-globin protein in adult hemoglobin due to mutations in the β (HBB) gene, leading to profound anemia. TDT patients require life-long red-cell transfusions and have impaired quality of life. TDT can also cause ineffective erythropoiesis in pediatric patients, which can lead to bone deformities and growth retardation (National Organization for Rare Disorders 2021; [2]Benz and Angelucci 2024).

The clinical management of TDT focuses on reducing anemia-related symptoms and consists of lifelong, regular (usually every 2 to 5 weeks) blood transfusions to maintain a pre-transfusion hemoglobin level above 9 g/dL and iron chelation therapy to remove excess iron introduced with transfusions. Transfusion-induced iron overload causes widespread organ damage, most notably affecting the cardiac, hepatic, and endocrine system and is the predominant cause of morbidity and mortality. Allogeneic hematopoietic stem cell transplantation (HSCT) was the only permanent curative option for TDT β-thalassemia patients, but only for those with an available HLA-matched donor.

As a result, the viability of a HSCT is limited by a lack of suitable donors. Gene therapy, which involves the autologous transplantation of genetically modified hematopoietic stem cells, is currently a novel therapeutic option.

Zynteglo (betibeglogene autotemcel; beti-cel) is an ex vivo gene therapy that utilizes a lentiviral vector (LVV) to introduce a modified *β*-globin$^{A\text{-}T87Q}$ gene into autologous hematopoietic stem cells. Zynteglo is a sustainable and potentially curative alternative to chronic transfusion. Once the $\beta^{A\text{-}T87Q}$-globin gene of Zynteglo is incorporated, hematopoietic stem cells have the potential to produce HbA^{T87Q}, the gene therapy-derived adult Hb, at levels that can eliminate or significantly reduce the need for transfusions. The goal of beti-cel treatment is to correct ineffective erythropoiesis and enable lifelong, stable production of functional adult hemoglobin at levels sufficient to result in transfusion independence (TI).

TI was achieved in the majority of non-β0/β0 TDT patients; however, the long-term impact of beti-cel on other clinically relevant outcomes, such as overall survival, is unknown at this time. Due to the significant risks associated with myeloablative conditioning therapy and the requirement that Zynteglo be administered in a specialized center with stem cell transplantation expertise, it is likely that the therapy will be reserved for patients with severe disease who cannot be effectively managed with transfusions and chelation therapy (with or without Reblozyl) as an alternative to HSCT.

Both non-β0/β0 TDT (n=13) and β0/β0 TDT (n=9) patients were enrolled in the earliest trials (Northstar and HGB-205). Only 33% of patients with β0/β0 TDT (3/9) were successful in achieving TI, compared to 92% of patients with non-β0/β0 TDT (12/13). Therefore, the use of beti-cel for TDT β0/β0 genotype is considered experimental until additional data is published in a peer reviewed journal.

COVERAGE POLICY

All Gene Therapy requests require Molina Medical Director review.

Zynteglo (beti-cel) for the treatment of TDT may be **considered medically necessary** when **ALL** the following clinical criteria with documentation are met:

1. A diagnosis of β-thalassemia with genetic confirmation of non-β0/β0
2. Member has **transfusion dependent disease** managed under standard thalassemia guidelines and documented by **ONE** of following **(a or b):**
    a. Receipt of ≥ 8 transfusions of packed red blood cells (pRBC) per year in the two previous years
    b. Receipt of at least 100 mL/kg/year of pRBCs in the two previous years
3. Age ≥ 4 years and ≤ 50 years at the time of infusion
4. A human leukocyte antigen (HLA)-matched related HSC donor is not available
5. No prior hematopoietic stem cell transplant (HSCT)
6. Clinical documentation with recent relevant evaluation including labs, and workup establishing eligibility for Zynteglo gene therapy must include the following:
    a. Member is clinically stable and eligible for an allogeneic HSCT, and has Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (ambulatory and able to carry out work of a light or sedentary nature); OR Karnofsky or Lansky performance status (KPS) of at least 80
    b. Adequate and stable renal, hepatic, and cardiac function. Members with ANY of the following labs or imaging do not meet criteria:
        i. Renal impairment defined as creatinine clearance ≤ 70 mL/min/1.73 m^2
        ii. Patients with a MRI or liver biopsy demonstrating bridging fibrosis, cirrhosis, or active hepatitis
        iii. Cardiac MRI findings of excess myocardial iron: T2* less than 10 milliseconds (msec)
        iv. Any other evidence of severe iron overload, such as MRI findings in the liver or abnormal serum iron/ferritin studies
        Note: In clinical trials, MRI of the liver was performed on all patients. Patients older than 18 years with MRI

results demonstrating liver iron content ≥ 15 mg/g underwent liver biopsy for further evaluation. Patients younger than 18 years with MRI results demonstrating liver iron content ≥ 15 mg/g were excluded from the studies unless a liver biopsy (at the discretion of the investigator) could provide additional data to confirm eligibility.

c. A negative serology test for Human Immunodeficiency Virus (HIV)
d. Member has not received, or is being considered for other gene therapy, or investigational cellular therapy for β-Thalassemia
g. Females of childbearing potential and males capable of fathering a child: Member has been counseled on the use of effective contraception during treatment (from start of mobilization through at least 6 months after administration of Zynteglo) and advised of the risks associated with conditioning agents
h. Females of childbearing potential must not be pregnant or breastfeeding, AND must have a documented negative serum pregnancy test within the past 30 days
NOTE: A negative serum pregnancy test must be confirmed prior to the start of mobilization and re-confirmed prior to conditioning procedures and before Zynteglo administration.

7. No history of uncorrected bleeding disorder

8. No history of prior or current malignancy

9. No history of advanced liver disease

10. The member is not positive for the presence of Hepatitis B virus (HBV), hepatitis C virus (HCV), human T-lymphotrophic virus 1 & 2 (HTLV-1/HTLV-2), and HIV-1 / HIV-2
NOTE: If a patient requires anti-retrovirals for HIV prophylaxis, then a negative test for HIV must be confirmed before beginning mobilization and apheresis of CD34+ cells

CONTINUATION OF THERAPY

The safety and efficacy of repeat treatment has not been studied and is currently not supported by any compendia nor indicated in the current FDA approved labeling. Requests for reauthorization or beyond one dose is considered experimental and will not be authorized.

Repeat administration is experimental and investigational since the safety and efficacy beyond one treatment has not been studied and is not indicated in the current FDA approval for Zynteglo. The evidence is insufficient to determine the effects on net health outcomes.

LIMITATIONS AND EXCLUSIONS

There are no contraindications listed in the manufacturer's labeling at this time. The following are considered **exclusions** based on insufficient evidence:

1. Prior treatment with Zynteglo, or being considered for treatment with other gene therapy

The following are considered **experimental, investigational, and unproven** based on insufficient evidence:

1. Any indications other than those listed above (e.g., sickle cell disease)
2. Prior treatment with any form of HSCT, Zynteglo, or other gene therapy

DURATION OF APPROVAL: Duration sufficient for **ONE** single course of treatment

PRESCRIBER REQUIREMENTS: Prescribed by, or in consultation with, a board-certified hematologist

DOSING CONSIDERATIONS: Cell suspension for IV infusion. For autologous use only.

- Patients are required to undergo HSC mobilization followed by apheresis to obtain CD34+ cells for Zynteglo manufacturing.
- Dosing is based on the number of CD34+ cells in the infusion bag(s) per kg of body weight. Minimum recommended dose: 5 x 10^6 CD34+ cells/kg as a one-time IV infusion
- Full myeloablative conditioning must be administered before infusion of Zynteglo.

QUANTITY LIMITATIONS: ONE (1) single treatment course of Zynteglo per lifetime. Additional infusions of Zynteglo will not be authorized.

ADMINISTRATION:

1. Zynteglo is considered a provider-administered therapy. It should be administered in a Qualified Treatment Center by a physician(s) with experience in HSCT and in the treatment of patients with TDT.
2. Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or rendering a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

The Biologics License Application (BLA) for Zynteglo is supported by results from the Phase 3 trials, Northstar-2 (HGB-207) and Northstar-3 (HGB-212), the Phase 1/2 studies Northstar HGB-204 and HGB-205, and a Phase 4 long-term follow-up study (LTF303). A total of 63 patients have undergone gene therapy: 57 patients had completed 2 years of follow-up (22 treated in Phase 1/2 studies, 35 treated in Phase 3 studies); 20 patients had completed 5 years of follow-up, 11 patients with at least 6 years of follow-up, and 3 patients with up to 7 years of follow-up across β0/β0 and non-β0/β0 genotypes.

Phase 1/2 Studies

HGB-204 and **HGB-205,** two single-arm, phase 1/2 trials, evaluated the safety and efficacy of single-dose beti-cel in a total of 22 patients with TDT of any genotype: both non-β0/β0 TDT (n=13) and β0/β0 TDT (n=9) patients. Participants were 35 years of age or younger, with lower age limits of 12 and 5 years in the HGB-204 (n=18) and HGB-205 (n=4) trials, respectively. Patients were deemed transfusion-dependent if they received at least 8 transfusions per year, or at least 100 mL/kg of body weight of packed red cells per year, in the two years prior to enrollment. Of the 23 enrolled patients in these two trials who underwent mobilization and apheresis, all but one patient continued on to receive beti-cel. The reported AEs were similar to those associated with autologous stem cell transplantation, and no identified safety issues were related to the LVV used in the manufacture of gene therapy, according to the researchers (Thompson et al. 2018).

These trials were primarily designed for safety and engraftment endpoints, but Magrin et al. (2022) also reported early results of HGB-205 on 4 participants receiving betibgelogene for TDT. All four patients in HGB-205 receiving betibgelogene for TDT were transfusion independent at the time of publication. Three patients had non-β0/β0 genotype and the fourth was homozygous B^+ IVS1-110. Kwiatkowski et al. (2019) reported very initial results from HGB-204 indicating 3 of 8 participants with β0/β0 genotype achieved transfusion independence compared to 8 of 10 for non-β0/β0 genotype. Long term follow-up data from these trials are below under LTF-303 trial data.

Phase 3 Studies

NorthStar-2 (HGB-207) and **NorthStar-3 (HGB-212)** were identically designed phase 3 open-label, single-arm, 24-month studies in TDT β-thalassemia. NorthStar-2 enrolled patients with a non-β0/β0 genotype, while NorthStar-3 enrolled patients with a β0/β0 genotype or severe non-β0/β0. Patients were eligible if they were up to 50 years old, transfusion dependent (at least 8 transfusions annually for the previous two years, or at least 100 mL/kg/year of packed red blood cells), and were HSCT-eligible. Patients who had a previous HSCT or a known or available HLA-matched family donor were excluded. These two trials used the most recent formulation of beti-cel.

Northstar-2 (NCT02906202) details: The efficacy and safety of beti-cel was evaluated in 23 adult and pediatric patients (n=23) with TDT β-thalassemia and a **non-β0/β0** genotype. A total of 23 patients ages 4 to 34 years were treated, with a median follow-up duration of 29.5 months (range: 13.0 to 48.2). Prior to the infusion of beti-cel, patients undergo myeloablative chemotherapy, as with HSCT. Patients in this trial were hospitalized for an average of 45 days and underwent myeloablation with busulfan (with doses adjusted based on pharmacokinetic analysis) and then received beti-cel intravenously.

The **primary end point** was TI (the weighted average hemoglobin level of ≥ 9 g per deciliter without red-cell

transfusions for ≥12 months). Only 19 patients were evaluable for TI (the other participants were not followed up for sufficient time yet) and 89% (17/19) of patients achieved TI, with median weighted average total Hb levels of 11.9 g/dL (min-max: 9.4 – 12.9 g/dL). Before gene therapy these 17 patients required between 11.5 to 37 transfusions per year. The beti-cel safety profile was comparable to that of busulfan-based myeloablation. At least one AE assessed by the investigators to be due to or possibly associated to beti-cel occurred in 4 patients; all occurrences were nonserious except for thrombocytopenia (in 1 patient). There were no observed cases of cancer. There were no confirmed cancer cases (Locatelli et al. 2022). Per study information reported in the FDA label 7 participants that achieved transfusion independence continued phlebotomy for iron removal.

Northstar-3 (NCT03207009) details: This phase three trial enrolled 18 patients with either a **β0/β0** genotype or **IVS-I-110** mutation. Fifteen patients ages 4 to 33 years (genotypes: 9 β0/β0, 3 β0/β+ IVS1-110, 3 homozygous IVS-1-110 mutation) were treated and had a median follow-up of 14.4 months.

The **primary endpoint** was transfusion independence. Six of the 8 of evaluable patients achieved TI, with median weighted average total Hb levels of 11.5 g/dL (min-max: 9.5 – 13.5 g/dL) and continued to maintain TI for a median duration of 13.6 months. At the time of data cutoff, 85% of patients (11/13) with at least 7 months of follow-up had not received a transfusion in more than seven months. Previously, these 11 patients required an average of 18.5 transfusions per year (min to max: 11.0 to 39.5 transfusions per year). At the last visit, beti-cel gene therapy-derived HbAT87Q supported total Hb levels ranging from 8.8-14.0 g/dL. Two adverse events of fever post-infusion were reported.

Phase 4 Long-Term Follow-Up

LTF-303 (NCT02633943) is a multi-center phase 4 long-term follow-up study that included patients from the four trials (HGB-204, HGB-205, HGB 207, and HGB212). After participating in and completing the two-year follow-up in either phase 1/2 studies (HGB-204, HGB-205) or one of the phase 3 studies (HGB-207, HGB-212), patients were invited to enroll in the 13-year long-term follow-up study. Patients were initially followed every 6 months for the first 5 years following product infusion, and then annually from Year 5 to Year 15. Patients have been followed for an average of 42 months and up to 87 months.

- The interim results of 32 patients have shown that 64% of the patients from the HGB-204/HGB-205 studies and 90% of the patients of the HGB 207/HGB-212 studies achieved durable and stable TI (Kwiatkowski et al. 62nd ASH Annual Meeting, 2020).
- Interim results from the HGB-207 and HGB-212 trials in pediatric patients showed that children achieved TI at comparable rates and with comparable safety to adults (Thompson et al. 62nd ASH Annual Meeting, 2020).

There have been no deaths, no vector-derived replication-competent lentivirus, and no events of insertional oncogenesis or malignancy reported to date. Furthermore, there is an absence of drug product-related AEs beyond 2 years post-infusion. [Cut-off date: Aug 18, 2021]

Magrin et al. (2022) published the findings of long-term outcomes of 4 TDT patients who completed the HGB-205 trial and were subsequently enrolled in the LTF-303 study. All four patients have remained transfusion-free with no beti-cel-related adverse events after a 6-year follow-up for two patients and a 4-year follow-up for two patients (median, 4.5).

National and Specialty Organizations

Thalassaemia International Federation (TIF)
TIF reviewed the evidence and addressed gene therapies for TDT treatment in its 2021 Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT), and TIF noted the following regarding Zynteglo (beti-cel) (Cappellini et al. 2023):

LVV gene therapy is the most mature intervention among novel gene therapies, having been shown to provide clinical efficacy and safety as a one-time, life-changing treatment. However, the long-term safety and sustainability of the response must also be demonstrated; thus, treated patients are followed in 15-year follow-up trials.

According to the guidelines, *'it remains to be demonstrated in the long run and based on the percentage of patients becoming transfusion independent, developing a thalassaemia intermedia phenotype, or failing to respond, whether*

such a one-time expense will indeed be cost-effective overall, compared to the cumulative costs of lifelong conventional treatment of the disease and its complications.'

Furthermore, patients with *β*-thalassemia major may be eligible for the following treatments while awaiting long-term clinical data on gene therapy for β-thalassemia. These treatments are presently available and are based on accepted indications.

i. Allogeneic HSC transplantation: young patients (≤ 17 years old) with a β+ or β0 genotype having an HLA-compatible sibling or a 10/10 matched volunteer donor
ii. Gene therapy with Zynteglo: young patients (> 12 < 17 years old) with a β+ genotype who do not have an HLA-compatible sibling donor
iii. Gene therapy with Zynteglo: patients > 17 ≤ 55 years old with a β+ genotype who do not have severe comorbidities and are at risk or ineligible to undergo an allo-HSC transplant but can otherwise undergo an autologous gene therapy procedure with an acceptable risk.

Institute for Clinical and Economic Review (ICER) published a final evidence report supporting the long-term value of beti-cel for the treatment of beta thalassemia (July 2022). The report focused on the clinical benefits of beti-cel and its cost-effectiveness compared to standard clinical management for TDT beta thalassemia, which includes lifelong blood transfusions and iron chelation therapy. The systematic review comprised 5 studies of beti-cel: two phase 1/2 trials (HGB-204 and HGB-205), two phase 3 trials (NorthStar 2 and NorthStar 3), and one cohort study that followed trial participants over the long duration (LTF-303). All 4 trials were open-label, single-arm studies. The evidence suggests beti-cel is generally superior to standard of care for patients with β-thalassemia, but the magnitude of this superiority is still uncertain due to known risks with myeloablative conditioning and unknown durability. Even if beti-cel proves to be a long-lasting treatment with an excellent safety profile, many patients will likely continue transfusion and chelation, according to the authors.

In the phase 3 trials, 90% of patients (n = 56) achieved and maintained TI for a median of 42 months. The LTFU indicated that independence from transfusion was maintained for a mean of 42 months (range: 23-87). The report notes that this duration is insufficient to confirm long-term durability, and while the analysis concludes that beti-cel is superior to the current standard of care, its long-term health benefits are unknown. Most of the serious AEs were attributable to known risks associated with myeloablative conditioning, the degree of risk of beti-cel infusion in real-world practice remains unknown. In light of these considerations, ICER assigned beti-cel gene therapy a rating of moderate certainty (incremental or better), which indicates a point estimate of small or substantial net health benefit.

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

Code	Description
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
96415	Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure)

HCPCS (Healthcare Common Procedure Coding System)

Code	Description
J3393	Injection, betibeglogene autotemcel, per treatment

AVAILABLE DOSAGE FORMS: Injection, suspension: minimum of 5 × 10^6 CD34+ cells/kg; Each infusion bag contains approximately 20 mL of Zynteglo.

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

12/11/2024	Added requirement of Molina Medical Director review.
10/09/2024	Annual review. Re-organized criteria under exclusions and limitations into inclusion criteria. No changes to indications.
10/12/2023	Annual review. No changes to coverage policy.
10/12/2022	New policy. IRO Peer Review. 8/26/2022. Policy reviewed by practicing physician Board-certified in Hematology & Oncology.

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