NEW DRUG APPROVAL

Brand Name	Zynteglo®
Generic Name	betibeglogene autotemcel
Drug Manufacturer	Bluebird Bio, Inc.

New Drug Approval

FDA approval date: August 17, 2022

Review designation: N/A

Type of review: Biologics License Application (BLA): 125717

Dispensing restriction: Limited Distribution; Specialty Only and Direct Purchase Only

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Thalassemias are a heterogeneous grouping of genetic disorders that result from a decreased synthesis of alpha or beta chains of hemoglobin (Hb). Hemoglobin serves as the oxygen-carrying component of the red blood cells. It consists of two proteins, an alpha, and a beta. If the body does not manufacture enough of one or the other of these two proteins, the red blood cells do not form correctly and cannot carry sufficient oxygen; this causes anemia that begins in early childhood and lasts throughout life. Thalassemia is an inherited disease, meaning that at least one of the parents must be a carrier for the disease. It is caused by either a genetic mutation or a deletion of certain key gene fragments.

Alpha thalassemia: Alpha thalassemia is caused by alpha-globin gene deletion which results in reduced or absent production of alpha-globin chains. Alpha globin gene has 4 alleles and disease severity ranges from mild to severe depending on the number of deletions of the alleles. Four allele deletion is the most severe form in which no alpha globins are produced and the excess gamma chains (present during the fetal period) form tetramers. It is incompatible with life and results in hydrops fetalis. One allele deletion is the mildest form and is mostly clinically silent.

Beta thalassemia: Beta thalassemia results from point mutations in the beta-globin gene. It is divided into three categories based on the zygosity of the beta-gene mutation. A heterozygous mutation (beta-plus thalassemia) results in beta-thalassemia minor in which beta chains are underproduced. It is mild and usually asymptomatic. Beta thalassemia major is caused by a homozygous mutation (beta-zero thalassemia) of the beta-globin gene, resulting in the total absence of beta chains. It manifests clinically as jaundice, growth retardation, hepatosplenomegaly, endocrine abnormalities, and severe anemia requiring life-long blood transfusions. The condition in between these two types is called beta-thalassemia intermedia with mild to moderate clinical symptoms.

Epidemiology: According to bluebird's estimates, approximately 1300–1500 individuals have TDT in the United States, of whom 850 could be eligible for treatment. The disorder is particularly prevalent in the Mediterranean, Middle East, Africa, Central Asia, the Indian subcontinent, and the Far East, and descendants from these areas.

Efficacy

Table 1 provides a list of clinical trials that support the use of Zynteglo®.

Table 1. Clinical Studies Supporting the Use of Zynteglo®

Study	NCT	Phase	Published Study
HGB-204 (Northstar)	NCT01745120	1/2	NEJM, 2018

HGB-205	NCT02151526	1/2	Nat Med, 2022
HGB-207 (Northstar-2)	NCT02906202	3	NEJM, 2022
HGB-212 (Northstar-3)	NCT03207009	3	N/A
LTF-303	NCT02633943	Long-term study*	Nat Med, 2022

Abbreviations: N/A, not applicable; NCT, National Clinical Trial.

*Long-term follow-up study 15 years post-treatment after completion of Studies HGB-204, -205, -207, or -212.

Northstar-2 and Northstar-3

The approval of Zynteglo was based on results from two registrational Phase 3, open-label, single-arm, 24-month, multicenter trials, Northstar-2 (HGB-207; NCT02906202) and Northstar-3 (HGB-212; NCT03207009), as well as the longterm follow-up study, LTF-303. Northstar-2 and Northstar-3 included a total of 41 patients with beta-thalassemia requiring regular transfusions.

Table 2 summarizes the overall design of Northstar-2 and Northstar-3 clinical trials.

Table 2. Zynteglo® Clinical Studies: Study Design Summary

	Northstar-2 (NCT02906202) N = 23	Northstar-3 (NCT03207009) N = 18
Study Design	Ongoing Phase 3, open-label, single-arm, 24-month, multicenter study evaluating the efficacy and safety of Zynteglo® in patients with TDT	
Study Population	• Genotype: non-β^0/β^0 • Median age: 15 years (range, 4–34 years) • 52% females; 48% males • Asian, 57%; White, 35%; Other/not reported, 9% • Baseline* transfusion volume, mL/kg/year: 208 (range, 142–274) • Baseline* transfusion frequency, transfusions per year: 16 (12–37)	• Genotype: β^0/β^0 or non-β^0/β^0 (n = 12 β^0/β^0; n = 6 non-β^0/β^0) • Median age: 13 years (range, 4–33 years) • 44% females: 56% males • Asian, 39%; White, 56%; Other/not reported, 6% • Baseline* transfusion volume, mL/kg/year: 194 (range, 75–289) • Baseline* transfusion frequency, transfusions per year: 17 (11–40)
Inclusion Criteria	• ≤50 years of age • TDT with history of ≥100 mL/kg/year of pRBCs or ≥8 transfusions of pRBCs per year in the 2 years preceding enrollment • Clinically stable and eligible to undergo HSCT	
Key Exclusion Criteria	• Presence of β^0 mutation at both alleles of β-globin gene • Known and available HLA-matched family donor • Any evidence of severe iron overload warranting exclusion†	• Presence of a mutation other than β^0 (e.g. β^+, β^E, β^C) on ≥1 β-globin gene allele • Known and available HLA-matched family donor • Any evidence of severe iron overload warranting exclusion†
Interventions	Zynteglo® administered by IV infusion following myeloablative conditioning with busulfan	

Primary Endpoints	Proportion of participants with TI‡
Key Secondary Endpoints	• Proportion of participants with TI‡ at Month 24 • Duration of TI‡ • Time taken for achievement of TI‡

Abbreviations: HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplant; IV, intravenous; pRBCs, packed red blood cells; TDT, transfusion-dependent beta-thalassemia; TI, transfusion independence.

*Baseline annualized based on data 2 years prior to enrollment.

†In the study investigator's opinion. ‡TI was defined as hemoglobin ≥9 grams g/dL without any pRBC transfusions for a continuous period of ≥12 months at any time during the study after drug product infusion.

Efficacy Results

Northstar-2 was conducted in 23 patients with beta-thalassemia requiring regular transfusions and with a non-β 0 /β0 genotype. The median (min, max) duration of follow-up was 29.5 (13.0, 48.2) months. Northstar-3 was conducted in 18 patients with beta-thalassemia requiring regular transfusions and a β0 /β0 or non-β 0 /β0 genotype. The median (min, max) duration of follow-up was 24.6 (4.1, 35.5) months.

In both studies, the efficacy of Zynteglo® was established based on achievement of TI, defined as a weighted average Hb ≥9 g/dL without any packed red blood cell (pRBC) transfusions for a continuous period of ≥12 months at any time during the study after infusion of Zynteglo®.

Table 3 summarizes the efficacy outcomes for patients treated with Zynteglo in Northstar-2 and Northstar-3.

Table 3. Efficacy Outcomes for Patients Treated with Zynteglo® Who Achieved Transfusion Independence

	Northstar-2* (N = 23)	Northstar-3* (N = 18)	Overall Results* (N = 41)
TI			
n/N†, (%)	20/22 (91%)	12/14 (86%)	32/36 (89%)
[95% CI]	[77, 99]	[57, 98]	[74, 97]
Weighted Average Total Hb During TI (g/dL)			
n	20	12	32
Median (min, max)	11.8 (9.7, 13.0)	10.2 (9.3, 13.7)	11.5 (9.3, 13.7)
Duration of TI (Months)‡			
n	20	12	32
Median (min, max)	NR (15.7+, 39.4+)	NR (12.5+, 32.8+)	NR (12.5+, 39.4+)

Abbreviations: CI, confidence interval; Hb, hemoglobin; NR, not reached; TI, transfusion independence.

*Includes duration of follow-up from LTF-303.

†N represents the total number of patients evaluable for TI, defined as patients who have completed their parent study (i.e. Month 24) or achieved TI, or who will not achieve TI in their parent study.

‡Based on Kaplan-Meier

Long-Term Outcomes: Information on long-term follow-up can be found in the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) meeting presentations. Up to 7 years of follow-up data have been reported, showing longer-term durability in a subset of patients.

Safety: In both Northstar-2 and Northstar-3, there were no cases of graft-versus-host disease (GVHD), graft failure, or graft rejection and all the patients were alive at the last follow-up. The safety profile is consistent with that of the mobilization and conditioning agents.

No malignancies or cases of insertional oncogenesis were seen with Zynteglo®. However, similar lentiviral vector (LVV) products being developed by bluebird, elivaldogene autotemcel (eli-cel) (in development for cerebral adrenoleukodystrophy [CALD]) and lovo-cel (in development for sickle cell disease [SCD]), have had cases of malignancy. In the clinical studies for eli-cel for CALD, 3/67 (4%) of patients developed myelodysplastic syndrome (MDS) and there were 4 additional cases of concern. In the trials for lovo-cel for SCD, 2/49 (4%) of patients developed cases of acute myeloid leukemia (AML) and there were 3 additional cases of concern.

Therefore, Zynteglo® has a labeled safety warning for insertional oncogenesis, with monitoring required. Safety information for all three products is limited by small sample sizes and their duration of follow-up.

Safety

ADVERSE EVENTS

Most common non-laboratory adverse reactions (incidence ≥20%): mucositis, febrile neutropenia, vomiting, pyrexia, alopecia, epistaxis, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus.

Most common Grade 3 or 4 laboratory abnormalities (>50%): neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia.

WARNINGS & PRECAUTIONS

Delayed Platelet Engraftment: Delayed platelet engraftment has been observed with Zynteglo® treatment. Bleeding risk is increased prior to platelet engraftment and may continue after engraftment in patients with prolonged thrombocytopenia; 15% of patients had ≥ Grade 3 decreased platelets on or after Day 100. Patients should be made aware of the risk of bleeding until platelet recovery has been achieved. Monitor patients for thrombocytopenia and bleeding according to standard guidelines. Conduct frequent platelet counts until platelet engraftment and platelet recovery are achieved. Perform blood cell count determination and other appropriate testing whenever clinical symptoms suggestive of bleeding arise.

Risk of Neutrophil Engraftment Failure: There is a potential risk of neutrophil engraftment failure after treatment with Zynteglo®. Neutrophil engraftment failure is defined as failure to achieve three consecutive absolute neutrophil counts (ANC) ≥ 500 cells/microliter obtained on different days by Day 43 after infusion of Zynteglo®. Monitor neutrophil counts until engraftment has been achieved. If neutrophil engraftment failure occurs in a patient treated with Zynteglo®, provide rescue treatment with the back-up collection of CD34+ cells.

Risk of Insertional Oncogenesis: There is a potential risk of lentiviral vector (LVV)-mediated insertional oncogenesis after treatment with Zynteglo®. Patients treated with Zynteglo® may develop hematologic malignancies and should be monitored lifelong. Monitor for hematologic malignancies with a complete blood count (with differential) at Month 6 and Month 12 and then at least annually for at least 15 years after treatment with Zynteglo®, and integration site analysis at Months 6, 12, and as warranted.

Hypersensitivity Reactions: Allergic reactions may occur with the infusion of Zynteglo®. The dimethyl sulfoxide (DMSO) in Zynteglo® may cause hypersensitivity reactions, including anaphylaxis.

Anti-retroviral and Hydroxyurea Use: Patients should not take prophylactic HIV anti-retroviral medications or hydroxyurea for at least one month prior to mobilization, or for the expected duration for elimination of the medications, and until all cycles of apheresis are completed. If a patient requires anti-retrovirals for HIV prophylaxis, then confirm a negative test for HIV before beginning mobilization and apheresis of CD34+ cells.

Interference with Serology Testing: Patients who have received Zynteglo® are likely to test positive by polymerase chain reaction (PCR) assays for HIV due to integrated BB305 LVV proviral DNA, resulting in a false-positive test for HIV. Therefore, patients who have received Zynteglo® should not be screened for HIV infection using a PCR-based assay.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS OF ACTION

Zynteglo® adds functional copies of a modified β-globin gene into patients' hematopoietic stem cells (HSCs) through transduction of autologous CD34+ cells with BB305 LVV. After Zynteglo® infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate to produce RBCs containing biologically active $\beta^{A\text{-}T87Q}$-globin (a modified β-globin protein) that will combine with α-globin to produce functional adult Hb containing $\beta^{A\text{-}T87Q}$-globin (HbAT87Q). $\beta^{A\text{-}T87Q}$-globin can be quantified relative to other globin species in peripheral blood using high-performance liquid chromatography. $\beta^{A\text{-}T87Q}$-globin expression is designed to correct the β/α-globin imbalance in erythroid cells of patients with β-thalassemia and has the potential to increase functional adult HbA and total Hb to normal levels and eliminate dependence on regular pRBC transfusions.

Dose & Administration

ADULTS

5.0×10^6 CD34+ cells/kg for one-time single-dose intravenous use only.

PEDIATRICS

Refer to adult dosing.

GERIATRICS

None

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Zynteglo® is a cell suspension for intravenous infusion. Zynteglo® is composed of up to four infusion bags which contain 2.0 to 20×10^6 cells/mL suspended in cryopreservation solution. Each infusion bag contains approximately 20 mL of Zynteglo®. A single dose of Zynteglo® contains a minimum of 5.0×10^6 CD34+ cells per kg of body weight, suspended in cryopreservation solution.