New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Zynteglo® (betibeglogene autotemcel) [bluebird bio, Inc.]**
Dosage Formulations:	Intravenous (IV) infusion containing a frozen suspension of genetically modified autologous cells, enriched for CD34+ cells.
FDA Approval Date: **FDB File Date:**	FDA: August 17, 2022 FDB: August 28, 2022
Indication:	Treatment of adult and pediatric patients with beta-thalassemia who require regular red blood cell (RBC) transfusions.
Mechanism of Action:	Zynteglo adds functional copies of a modified β-globin gene into a patient's own hematopoietic stem cells (HSCs) through transduction of autologous CD34+ cells with BB305 lentiviral vector (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 hemoglobin (HbA) containing $\beta^{A\text{-}T87Q}$-globin (HbA^{T87Q}). $\beta^{A\text{-}T87Q}$-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 HbA and total hemoglobin (Hb) to normal levels and eliminate dependence on regular packed RBC (pRBC) transfusions.

Dose/ Administration:	• Zynteglo is provided as a single dose for infusion containing a suspension of CD34+ cells in 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. The minimum recommended dose of Zynteglo is 5.0 × 10^6 CD34+ cells/kg body weight.
	• Before mobilization, apheresis, and myeloablative conditioning are initiated, confirm that hematopoietic stem cell transplantation (HSCT) is appropriate for the patient. It is recommended that patients be maintained at a Hb ≥ 11 g/dL for at least 30 days prior to mobilization and 30 days prior to myeloablative conditioning.
	• Patients are required to undergo HSC mobilization followed by apheresis to obtain CD34+ cells for product manufacturing. The target number of CD34+ cells to be collected is ≥ 12 × 10^6 CD34+ cells/kg. If the minimum dose of 5.0 × 10^6 CD34+ cells/kg is not met, the patient may undergo additional cycles of mobilization and apheresis, separated by at least 14 days in order to obtain more cells for additional manufacture.
	• A back-up collection of CD34+ cells of ≥ 1.5 × 10^6 CD34+ cells/kg (if collected by apheresis) or > 1.0 × 10^8 TNC/kg (Total Nucleated Cells, if collected by bone marrow harvest) is required. These cells must be collected from the patient and cryopreserved prior to myeloablative conditioning. The back-up collection may be needed for rescue treatment if there is:
	  ○ Compromise of hematopoietic stem cells or Zynteglo before infusion
	  ○ Primary engraftment failure
	  ○ Loss of engraftment after infusion of Zynteglo
	• Myeloablative Conditioning
	  ○ Full myeloablative conditioning must be administered before infusion of Zynteglo. Stop iron chelation at least 7 days prior to myeloablative conditioning. Prophylaxis for hepatic veno-occlusive disease is recommended. Prophylaxis for seizures should be considered, as appropriate.
	  ○ Do not begin myeloablative conditioning until the complete set of infusion bag(s) constituting the dose of Zynteglo has been received and stored at the treatment center and the availability of the back-up collection is confirmed. After completion of the myeloablative conditioning, allow a minimum of 48 hours of washout before Zynteglo infusion.
	• Zynteglo is shipped to the treatment center in a frozen state and must be stored according to product specifications. Coordinate the timing of Zynteglo thaw and infusion. Confirm the infusion time in advance and adjust the start time of Zynteglo thaw

	such that it will be available for infusion when the patient and healthcare providers are ready. • Zynteglo is for autologous use only. The patient's identity must match the patient identifiers on the Zynteglo cassette(s) and infusion bag(s). Product must be administered within 4 hours after thawing. Access the infusion bag and infuse Zynteglo as soon as possible after thawing and complete the infusion within 4 hours. Administer each infusion bag via intravenous infusion over a period of less than 30 minutes. If more than one infusion bag is provided, administer each infusion bag completely before proceeding to thaw and infuse the next infusion bag. Flush all Zynteglo remaining in the infusion bag(s) and any associated tubing with at least 50 mL of 0.9% sodium chloride. • Standard procedures for patient management after HSC transplantation should be followed after Zynteglo infusion.
Disease State Clinical Highlights:	• Beta-thalassemia is an inherited blood disorder caused by pathogenic variants in the β-globin (*HBB*) gene leading to impaired beta-globin protein production. Beta-globin is an important component of Hb, an oxygen-binding molecule found in erythrocytes that carries oxygen from the lungs to other tissues. Inadequate production of beta-globin results in the inability to produce appropriate levels of normal HbA. • Transfusion-dependent thalassemia (TDT), also known as thalassemia major or Cooley's syndrome, is one of the more severe forms of thalassemia due to greatly reduced levels of HbA. Patients generally require transfusions every 2 to 5 weeks resulting in decreased quality of life. Normal Hb concentrations are approximately 13.5 to 18 g/dL in men and 11.5 to 16 g/dL in women. In patients with TDT, Hb concentrations may be as low as 3 to 4 g/dL. • There are three major categories of *HBB* pathogenic variants, and patients are broadly defined as having either β^0/β^0 or non-β^0/β^0 genotypes. While β^0/β^0 genotype is most often associated with worse disease burden, patients with either genotype can be transfusion-dependent. ○ β^0 – no functional beta-globin production ○ β^+ – reduced functional beta-globin production ○ β^E – reduced functional beta-globin production resulting in variant Hb (HbE) • Clinical manifestation can vary widely and range from asymptomatic carrier status to severe disease burden including anemia, extramedullary hematopoiesis, skeletal and growth deficits, and iron overload resulting in a significant decrease in life expectancy. The median age of death for patients with TDT is 45 years. • The epidemiology of beta-thalassemia varies widely by ethnic populations. It most commonly occurs in Mediterranean, African, and Southeast Asian populations. According to bluebird bio, approximately 1,300-1,500 individuals have TDT in the United States of which 850 could be eligible for treatment with Zynteglo.
Drug Clinical Highlights:	• Zynteglo is the first cell-based gene therapy for the treatment for patients with beta-thalassemia who require regular RBC transfusions. <u>Contraindications</u>: none <u>Warnings/Precautions</u> • 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. Monitor patients for thrombocytopenia and bleeding according to standard guidelines. • 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 LVV-mediated insertional oncogenesis after treatment with Zynteglo. Patients treated with Zynteglo may develop hematologic malignancies and should be monitored lifelong. Monitor 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.
- 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. Patients who have received Zynteglo should not be screened for HIV infection using a PCR-based assay.

Drug Interactions:

- No formal drug interaction studies have been performed. Zynteglo is not expected to interact with the hepatic cytochrome P-450 family of enzymes or drug transporters.
- Live vaccines: The safety of immunization with live viral vaccines during or following Zynteglo treatment has not been studied.
- Antiretrovirals and Hydroxyurea: Patients should not take antiretroviral medications or hydroxyurea for at least one month prior to mobilization or the expected duration for elimination of the medications, and until all cycles of apheresis are completed. Antiretrovirals may interfere with the manufacturing of the apheresed cells.
- Iron Chelation: Iron chelators should be discontinued at least 7 days prior to initiation of conditioning. Some iron chelators are myelosuppressive. After Zynteglo 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.
- Erythropoiesis-stimulating agents: there is no clinical experience with the use of erythropoiesis-stimulating agents in patients treated with Zynteglo.

Pregnancy/Lactation:

- There are no available data with Zynteglo administration in pregnant women. It is not known whether Zynteglo has the potential to be transferred to the fetus, therefore it should not be administered to women who are pregnant.
- There is no information regarding the presence of Zynteglo in human milk, the effect on breastfed infants, and the effects on milk production. Therefore, Zynteglo is not recommended for women who are breastfeeding.

Clinical Studies

- Northstar-2 (HGB-207; NCT02906202) and Northstar-3 (HGB-212; NCT03207009): ongoing open-label, single-arm, 24-month, multicenter, registrational Phase 3 trials evaluating the efficacy and safety of Zynteglo.
  - Key Inclusion Criteria:
    - Participants ≤ 50 years of age at the time of consent. Participants younger than 5 years of age were enrolled if they weighed a minimum of 6 kgs and were

reasonably anticipated to be able to provide at least the minimum number of cells required to initiate the manufacturing process.
    - Diagnosis of TDT with a history of at least 100 mL/kg/year of pRBCs in the 2 years preceding enrollment (all participants) or ≥ 8 transfusions of pRBCs per year in the 2 years preceding enrollment (participants ≥ 12 years of age).
    - Clinically stable and eligible to undergo allogenic HSCT.
  - Key Exclusion Criteria:
    - Positive for presence of HIV, HBV, or HCV.
    - WBC count < 3×10^9/L and/or platelet count < 100×10^9/L not related to hypersplenism
    - Uncorrected bleeding disorder
    - Any prior or current malignancy
    - Prior HCST
    - Advanced liver disease
    - A cardiac T2* < 10 msec by MRI
    - Any evidence of severe iron overload that warrants exclusion
    - Prior receipt of gene therapy
    - Pregnancy
    - A known and available human leukocyte antigen (HLA) matched family donor
  - Key Baseline Characteristics:
    - Cardiac T2* mapping is a noninvasive MRI method that is used to identify myocardial iron accumulation. A cardiac T2* < 10 msec is associated with severe cardiac disease.
    - Karnofsky Performance Status is a widely used tool to assess a patient's functional status and ability to perform ordinary tasks. It ranges from 0 to 100 with a score of 100 representing a normal, healthy patient with no evidence of disease and a score of 0 representing death.

	Northstar-2 (N=23)	Northstar-3 (N=18)
Genotype	non-β^0/β^0	β^0/β^0 or non-β^0/β^0 (12 β^0/β^0; 6 non-β^0/β^0)
Age, years Median (min, max)	15 (4, 34)	13 (4, 33)
Sex	52% females; 48% males	44% females: 56% males
Race Asian White Other/Not Reported	57% 35% 9%	39% 56% 6%
Baseline[a] transfusion volume, mL/kg/year Median (min, max)	208 (142, 274)	194 (75, 289)
Baseline[a] transfusion frequency, transfusions per year Median (min, max)	16 (12, 37)	17 (11, 40)
Lansky or Karnofsky Performance Score All patients, minimum score Percentage of patients with score of 100	≥ 80 52%	≥ 90 56%
Cardiac T2* at baseline, msec Median (min, max)	37 (21, 57)	37 (15, 75)
Serum Ferritin at baseline, pmol/L Median (min, max)	4,438 (784, 22517)	3,275 (1279, 8874)
Liver Iron concentration at baseline, mg/g Median (min, max)	5.3 (1.0, 41.0)	3.6 (1.2, 13.2)

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

- Mobilization and Apheresis:
  - All patients were administered granulocyte-colony stimulating factor (G-CSF) and plerixafor to mobilize stem cells prior to the apheresis procedure. The planned dose of G-CSF was given in the morning on Days 1 through 5 of mobilization. The planned dose of plerixafor was given in the evening on Days 4 and 5 of mobilization. Apheresis generally occurred on mobilization Day 5 and 6 and if a third day of collection was needed, plerixafor and G-CSF dosing was extended to Day 6.
- Pre-treatment Conditioning:
  - All patients received full myeloablative conditioning with busulfan prior to treatment with Zynteglo. After completion of the 4-day course of busulfan, a washout period of at least 48 hours was required before Zynteglo administration.
- Zynteglo Administration:
  - All patients (N=41) were administered Zynteglo with a median (min, max) dose of 9.4 (5.0, 42.1) × 10^6 CD34+ cells/kg as an intravenous infusion.
- Primary Outcome Measure:
  - Achievement of transfusion independence (TI), defined as a weighted average Hb ≥ 9 g/dL without any pRBC transfusion for a continuous period of ≥ 12 months at any time during the study, after infusion of Zynteglo.
- Key Secondary Endpoints:
  - Weighted average total Hb during TI (g/dL)
  - Duration of TI (months)
  - Time taken for achievement of TI

Endpoint	Northstar-2 (N=23)	Northstar-3 (N=18)	Overall Results[a] (N=41)
Transfusion Independence (TI)[b] n/N[c] (%) [95% CI]	20/22 (91%) [77, 99]	12/14 (86%) [57, 98]	32/36 (89%) [74, 97]
Weighted Average Total Hb during TI (g/dL) n median (min, max)	20 11.8 (9.7, 13.0)	12 10.2 (9.3, 13.7)	32 11.5 (9.3, 13.7)
Duration of TI (months)[d] n median (min, max)	20 NR (15.7+, 39.4+)	12 NR (12.5+, 32.8+)	32 NR (12.5+, 39.4+)
Hb^{AT87Q} (g/dL) at Month 6 n median (min, max)	18 8.9 (5.2, 10.6)	11 8.9 (3.8, 12.0)	29 8.9 (3.8, 12.0)
Hb^{AT87Q} (g/dL) at Month 24 n median (min, max)	18 8.9 (5.0, 11.4)	8 9.8 (7.9, 12.4)	26 9.1 (5.0, 12.4)
Hb[e] (g/dL) at Month 6 n median (min, max)	20 11.7 (9.3, 13.3)	12 10.2 (8.8, 13.2)	32 11.4 (8.8, 13.3)
Hb[e] (g/dL) at Month 24 n median (min, max)	17 12.5 (9.5, 13.3)	9 10.9 (9.7, 14.0)	27 11.9 (9.5, 14.0)

[a]Includes duration of follow-up from Study 3.

[b]Transfusion independence (TI): a weighted average Hb ≥ 9 g/dL without any pRBC transfusions for a continuous period of ≥ 12 months at any time during the study after Zynteglo infusion.
[c]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 will not achieve TI in their parent study.
[d]Based on Kaplan-Meier.
[e]Hb levels are summarized for patients who do not have pRBC transfusions in the prior 60 days. NR = Not reached. Hb = Total Hb.

- In the Northstar-2 trial, the two patients who were evaluable for TI and did not achieve TI saw a reduction of 32% and 31% in transfusion volume requirements and a reduction of 20% and 26% in transfusion frequency. In the Northstar-3 trial, the two patients who were evaluable for TI and did not achieve TI saw a reduction of 92% and 3% in transfusion volume requirements and a reduction of 87% and 21% in transfusion frequency.
- Study 3 (NCT02633943) is a long-term follow-up study that includes 19 of the patients from Northstar-2 and 10 patients from Northstar-3. All patients remain alive at last follow-up, and there have been no cases of graft-versus-host disease, graft failure, or graft rejection.
- Adverse Reactions
  - Serious adverse reactions occurred in 37% of patients as of last follow-up. The most common adverse reactions (> 3%) were pyrexia, thrombocytopenia, liver veno-occlusive disease, febrile neutropenia, neutropenia, and stomatitis.
  - The most common adverse reactions (≥ 20%) were mucositis, febrile neutropenia, vomiting, pyrexia, alopecia, epistaxis, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritis.
  - The safety profile of Zynteglo was shown to be consistent with that of the mobilization and conditioning agents.

Price Per Unit (WAC):

$2.8 million per one-time infusion

Therapeutic Alternatives:

- According to the 2012 Standards of Care Guidelines for Thalassemia and 2021 Thalassaemia International Federation Guidelines, treatment for TDT consists of blood transfusion and iron chelation therapy to manage iron overload related to transfusions.
- HSCT offers a potential cure for TDT however it is associated with toxicities and transplant-related mortality, even for patients considered to be very good candidates. Lack of suitable donors and resources to provide HSCT present significant barriers for many patients. HSCT outcomes have been shown to be better in children and young adults with TDT compared to adults, overall thalassemia-free survival is > 85% in children and 65% in adults. According to the FDA Cellular, Tissue, and Gene Therapies Advisory Committee only 25% of TDT patients have a matched sibling donor.
- Reblozyl® was approved by the FDA in 2019 for the treatment of anemia in adult patients with beta-thalassemia who require regular blood transfusions. A comparison of Reblozyl and Zynteglo is provided below:

	Reblozyl	Zynteglo
Mechanism of Action	Erythroid maturation agent	Gene therapy
Dose	1 mg/kg subcutaneous injection every 3 weeks	One-time infusion
Notes	• Only indicated for adults • Shown to decrease transfusion frequency; 21.4% of patients treated with Reblozyl saw ≥ 33% reduction in transfusion burden with a reduction of at least 2 units for 12 consecutive weeks.	• Pediatric and adult patients • Shown to be achieve TI in 89% of patients.
Annual Cost Estimate	$186,269.00*	$2.8 million per one-time treatment

*Based on 75 kg participant receiving 1 mg/kg every 21 days (17 administrations per year)

Prior Authorization Approval Criteria:	**Must be the following criteria:**
	
	Initial Criteria:
	• Prescribed by or in consultation with a hematologist or other specialist in the treated disease state **AND**
	• Participant is not currently pregnant **AND**
	• Participant aged 5 to 50 years **OR**
	• For participants aged < 5 years:
	  ○ Participant weighs ≥ 6 kg **AND**
	  ○ Documentation of prescriber attestation that participant is reasonably anticipated to be able to provide at least the minimum number of cells required to initiate manufacturing process **AND**
	• Documented diagnosis of beta-thalassemia (ICD10 D56.1) confirmed by genetic testing **AND**
	• Participant considered to be transfusion-dependent defined by:
	  ○ Documented history of ≥ 100 mL/kg/year of pRBCs in the past two years **OR**
	  ○ For participants aged ≥ 12 years: ≥ 8 transfusions of pRBCs per year in the 2 years preceding enrollment **AND**
	• Participant lacks known and available HLA-matched family donor for HSCT **AND**
	• Participant lacks history of HSCT **AND**
	• Prescriber attestation that participant is clinically stable and eligible to undergo HSCT
	
	Continuation Criteria:
	• None
	
	Additional Provider Diagnostic/Monitoring Criteria, if desired:
	• Zynteglo has not been studied in patients with a history of HIV infection, HBV infection, or HCV infection.
	• Patients are advised not to take antiretrovirals or hydroxyurea during Zynteglo mobilization and treatment. If a patient requires antiretrovirals for the prevention of HIV, confirm a negative HIV test before initiating treatment with Zynteglo.
	• There is a potential risk of LVV-mediated insertional oncogenesis after treatment with Zynteglo. Monitor 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.

Implication to State Medicaid Program:	• Zynteglo will be available through a network of qualified treatment centers. bluebird bio is currently in the process of bringing these treatment center online with the goal of initiating apheresis in 4Q 2022 and infusions beginning in 1Q 2023. Currently there is no information regarding the locations of any of the treatment centers on the manufacturer's website. • With a price of $2.8 million, Zynteglo is one of the most expensive single-dose medications on the market. The Institute of Clinical and Economic Review (ICER) published an evidence report on Zynteglo in July of 2022, which concluded that the medication would be cost-effective if priced at $2.1 million with an 80% payback option if participants did not achieve and maintain TI over a 5-year period. • Treatment-related costs such as hospital stay could add an additional $100,000 per treatment. Patients receiving Zynteglo will need to stay in the hospital for 3 - 6 weeks after infusion. In addition, various other visits will be required, including pre-procedure visits, hyper transfusion, apheresis, and myeloablative conditioning. The ICER Final Evidence Report provided a summary of the additional treatment-related resource utilization and costs (see table below). In the Northstar-2 trial, the duration of hospitalization was a median of 45 days (range, 30–92 days) from conditioning to

discharge. It is possible that hospitalization could be longer, particularly depending on how patients tolerate the myeloablative conditioning.

Resource Use Associated with Zynteglo Therapy	Duration
Pre-procedure visits and tests*	N/A
Pre-transplant hyper transfusion	90 days
Filgrastim for mobilization	5 days
Filgrastim home administration	5 days
Plerixafor for mobilization	2 days
Apheresis procedure	1 day
Hospitalization for apheresis procedure	1 day
Prophylaxis for veno-occlusive disease (Ursodeoxycholic acid)	90 days
Prophylaxis for seizures (levetiracetam)	6 days
Fertility preservation	N/A
Myeloablative conditioning with busulfan	4 days
Hospitalization for conditioning	At least 6 days
Hospitalization for infusion/post-infusion	3 to 6 weeks
Post-infusion monitoring	Years 1-6

*Pre-procedure tests include: one outpatient visit, one blood test, one genotyping test, one liver biopsy, and one bone marrow analysis.

- Exagamglogene autotemcel (CRISPR Therapeutics/Vertex), better known as exa-cel, is another gene therapy currently in development for beta-thalassemia and sickle cell disease (SCD). Utilizing a gene editing technique known as CRISPR-Cas9, exa-cel genetically modifies defective genes in TDT and SCD.
  - NCT03655678: single-arm, multisite, single-dose Phase1/2/3 trial evaluating the safety and efficacy of exa-cel in TDT patients.
  - 42/44 patients with TDT demonstrated TI.
  - CRISPR/Vertex plan to submit a Biologics License Application (BLA) at the end of 2022 for potential approval in 2023.
- Pyrukynd® (mitapivat) was FDA-approved in February of 2022 for the treatment of pyruvate kinase deficiency. It is currently in Phase 3 trials for both thalassemia and SCD.
  - NCT03692052: Phase 2, open-label trial studying mitapivat in non-transfusion-dependent (non-TDT) alpha- and beta-thalassemia.
    - Of the 20 patients enrolled in the study, 80% met the primary endpoint of Hb response (≥1.0 g/dL increase from baseline).
  - ENERGIZE (NCT04770753) and ENERGIZE-T (NCT04770779) are ongoing Phase 3 trials evaluating mitapivat in non-TDT and TDT patients, respectively. These trials were initiated in November 2021, with a potential approval of 2025.

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