Medical Policy

BlueCross BlueShield Kansas
An Independent licensee of the Blue Cross Blue Shield Association

Title: Zynteglo (betibeglogene autotemcel) Medical Drug Criteria Program Summary

Professional / Institutional
Original Effective Date: November 15, 2022
Latest Review Date: October 8, 2024
Current Effective Date: November 15, 2022

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Zynteglo® (betibeglogene autotemcel) Suspension for intravenous infusion	Treatment of adult and pediatric patients with ß-thalassemia who require regular red blood cell (RBC) transfusions		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Beta thalassemia	Thalassemia is a rare genetic disease that is most common in Mediterranean regions and South and Southeast Asia. In recent years, the occurrence of thalassemia disorders has become more prevalent in the United States due to immigration patterns.(2) This disease can be further classified as Beta or Alpha depending on where the gene mutation is located. As a result of the mutation, the balance between Alpha and Beta globin chains is disrupted leading to the dysfunction of hemoglobin production. Patients that have β-thalassemia major or transfusion dependent thalassemia (TDT) require lifelong blood transfusions. Beta0 thalassemia refers to the absence of production of Beta globin. When patients are homozygous for the Beta0 thalassemia gene, they cannot make any functional Beta chains. Beta+ thalassemia indicates a mutation that presents as decreased but not absent production of Beta globin. Thalassemia patients in which one or both of their Beta thalassemia mutations are Beta+ mutations make some hemoglobin A, which results in a less severe form of the disease.(2) Prior to consideration of transfusion therapy, it is critical to confirm the patient's diagnosis. In addition to complete blood count (CBC), hemoglobin electrophoresis is the first diagnostic test. Fractions of hemoglobin A, A2, F, H, E, and other variants are measured. Mutations may overlap on the screening test, resulting in incorrect diagnosis or a false negative. Therefore, genetic analysis for both Beta thalassemia and Alpha thalassemia mutations is necessary.(2) Blood transfusion is the mainstay of care for individuals with thalassemia major and many with intermedia (i.e., less severe disease form). The purpose of transfusion is twofold: to improve anemia and to suppress ineffective erythropoiesis. Chronic transfusions prevent most of the serious growth, skeletal, and neurological complications of thalassemia major. The decision to start transfusions is based on the inability to compensate for low hemoglobin (signs of increased cardiac effort, tachycardia, sweating, poor feeding, and poor growth), or less commonly, increasing symptoms of ineffective erythropoiesis (bone changes, massive splenomegaly).(2) Blood transfusions are required when the initial hemoglobin level is well below 6 g/dL. However, patients with a hemoglobin level less than 7 g/dL may sometimes require regular transfusions if additional signs and symptoms of disease severity are present. The primary goal of transfusion is to shut off erythropoiesis. Transfusions should generally be given at an interval of three to four weeks, and with aging patients every 2 weeks may be necessary. The amount of blood received on transfusion day is determined by pre-transfusion hemoglobin levels. The target is to maintain pre-transfusion hemoglobin levels between 9 and 10 g/dL and post transfusion hemoglobin levels should not exceed 14 g/dL.(2)
Gene therapy	In recent years, the major advancement in the treatment of thalassemia has been targeted gene therapy. For years, the only curative treatment was allogenic bone marrow transplant, which was limited to young patients with well matched donors and the requirement for long-term immunosuppression to prevent or treat transplant related immunological complications such as graft-vs-host disease (GvHD) and rejection.(3) Gene therapy aims to provide a cure for thalassemia through the manipulation of the genome of hematopoietic stem cells, thus compensating for the inadequate or faulty function of the mutated genes. This can be achieved in one of two ways. One approach is by gene addition via a semi-random insertion of a healthy copy of

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<tr><td></td><td>the therapeutic gene into the cells using viral vectors. The second approach is gene editing via a precisely directed mutation that repairs the gene in situ or induces a disease-modifying effect (i.e., reactivation of hemoglobin (Hb) F synthesis) using site-specific nucleases.(3)

The most developed gene therapy approach currently is gene addition. Gene therapy by gene addition is the transfer of a healthy copy of the β (or γ) globin gene along with its important regulatory genomic elements into target-cells using modified viral constructs as delivery vehicles. After many years of preclinical evaluation, self-inactivating lentiviral vectors (SIN-LVs) have proven to be the safest and most effective means of delivery.(3)

Gene editing strategies for β thalassemia have primarily focused on inducing reactivation of the γ globin gene, aiming to correct the imbalance of the α-like/β-like globin chain ratio, the main pathophysiological cause of the disease. This can be achieved by inhibiting factors that repress the expression of the γ globin gene (i.e., BCL11A), thus mimicking hereditary persistence of fetal hemoglobin (HPFH) in which high levels of Hb F are maintained throughout adult life and compensate for the low levels of β globin expression in patients carrying thalassemic mutations. Disrupting the binding site or the enhancer of BCL11 causes upregulation of HbF to therapeutic levels. This approach is currently being investigated and clinical trials are ongoing.(3)</td></tr>
<tr><td>Efficacy</td><td>The efficacy of Zynteglo was evaluated in two phase 3 open-label, single-arm, 24-month, multicenter studies (Study 1 - NCT02906202 & Study 2 - NCT03207009). The primary outcome measure for both studies was the percentage of participants who achieved transfusion independence (TI). TI was defined as a weighted average hemoglobin (Hb) greater than or equal to 9 (g/dL) without any packed red blood cell (pRBC) transfusions for a continuous period of greater than or equal to 12 months at any time during the study after drug product infusion. Overall, across both studies 89% (32/36) of patients were able to achieve TI.(1)

Further clinical phase I/II studies have been initiated to include adults and adolescents with β thalassemia (HGB-204), sickle cell disease (SCD) (HGB-206) or with either β thalassemia or SCD (HGB-205). In the HGB-204 and HGB-205 trials 15 of 22 patients with β thalassemia became transfusion independent whereas seven had a median 73% reduction (range 19-100%) in transfusion requirements. The majority of patients (6/7) in whom best response was reduction in the number or/and the volume of transfusions belonged to the β0 genotype. In contrast, transfusion independence was achieved predominantly in patients having a non-β0/β0 genotype (12/15) over those carrying β0/β0 or 2 copies of IVSI-110 mutations (3/9). The lower vector copy number (VCN) in peripheral blood as compared to the drug product VCN, indicating low engraftment of transduced cells, was strongly correlated with the lower therapeutic benefit in the β0 patients. A subsequent transduction refinement was introduced in the manufacturing process of the phase III HGB-207 (non-β0/β0 genotypes) and HGB-212 (β0/β0 genotypes or double IVSI[1]110 mutations).(3)

Clinical trial criteria:(4-8)

<table>
<tr><td></td><td>HGB 204</td></tr>
<tr><td>Inclusion Criteria</td><td>• Participants between 12 and 35 years of age, inclusive, at the time of consent/assent, and able to provide written consent/assent, if applicable.</td></tr>
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		• Diagnosis of β-thalassemia major and a history of at least 100 mL/kg/year of pRBCs or greater than or equal to 8 transfusions of pRBCs per year for the prior 2 years. • Eligible for allogeneic bone marrow transplant. • Treated and followed for at least the past 2 years in a specialized center that maintained detailed medical records, including transfusion history.
	Exclusion Critiera	• Positive for presence of human immunodeficiency virus type 1 or 2 (HIV 1 and HIV 2). • A white blood cell (WBC) count less than 3 × 10^9/L, and / or platelet count less than 100 × 10^9/L if not due to hypersplenism. • Uncorrected bleeding disorder. • Any prior or current malignancy or myeloproliferative or immunodeficiency disorder. • Immediate family member with a known or suspected Familial Cancer Syndrome (including but not limited to hereditary breast and ovarian cancer syndrome, hereditary non-polyposis colorectal cancer syndrome and familial adenomatous polyposis). • Receipt of an allogeneic transplant. • Advanced liver disease, including persistent aspartate transaminase (AST), alanine transaminase (ALT), or total bilirubin value greater than 3 × the upper limit of normal, liver biopsy demonstrating cirrhosis, extensive bridging fibrosis, or active hepatitis. • Kidney disease with a calculated creatinine clearance less than 30% normal value. • Uncontrolled seizure disorder. • Diffusion capacity of carbon monoxide (DLco) less than 50% of predicted (corrected for hemoglobin).

		• A cardiac T2* less than 10 ms by magnetic resonance imaging (MRI). • Any other evidence of severe iron overload that, in the Investigator's opinion, warrants exclusion. • Clinically significant pulmonary hypertension, as defined by the requirement for ongoing pharmacologic treatment or the consistent or intermittent use of supplemental home oxygen. • Participation in another clinical study with an investigational drug within 30 days of Screening. • Any prior or current malignancy or myeloproliferative disorder. • Prior receipt of gene therapy.
	HGB 205	
	Inclusion Criteria	• Be between 5 and 35 years of age, inclusive. • Have severe SCD or transfusion dependent beta-thalassemia major, regardless of the genotype with the diagnosis confirmed by Hb studies. Transfusion dependence is defined as requiring at least 100 mL/kg/year of packed red blood cells (pRBCs). • Be eligible for allogeneic hematopoietic stem cell transplant (HSCT) based on institutional medical guidelines, but without a matched related donor. • Be willing and able, in the Investigator's opinion, to comply with the study procedures outlined in the study protocol. • Have been treated and followed for at least the past 2 years in a specialized center that maintained detailed medical records, including transfusion history. • Participants with severe SCD also must: • Have failed to achieve adequate clinical benefit following

			hydroxyurea treatment with sufficient dosage, for at least 4 months unless this treatment was not indicated or not well tolerated. • Have 1 or more of the following poor prognostic risk factors: o Recurrent vaso occlusive crises (at least 2 episodes in the preceding year or in the year prior to start of a regular transfusion program). o Presence of any significant cerebral abnormality on magnetic resonance imaging (MRI) (such as stenosis or occlusions). o Stroke without any severe cognitive disability. o Osteonecrosis of 2 or more joints. o Anti-erythrocyte alloimmunization (greater than 2 antibodies). o Presence of sickle cell cardiomyopathy documented by Doppler echocardiography. o Acute chest syndrome (at least 2 episodes) defined by an acute event with pneumonia-like symptoms (e.g., cough, fever [>38.5°C], acute dyspnea, expectoration, chest pain, findings upon lung auscultation, tachypnea, or wheezing) and the presence of a new pulmonary infiltrate. Participants with a chronic oxygen saturation <90% (excluding periods of SCD crisis) or carbon monoxide diffusing capacity (DLco) less than 60% in the absence of an infection should not be included in the study.

		• Participants with severe SCD and cerebral vasculopathy (defined by overt stroke; abnormal transcranial Doppler [> 170 cm/sec]; or occlusion or stenosis in the polygon of Willis; or presence of Moyamoya disease) may be enrolled only with approval by the Comite de Surveillance after review of safety and efficacy data from >or= 2 SCD participants without cerebral vasculopathy treated with LentiGlobin BB305 Drug Product
	Exclusion Criteria	• Availability of a willing 10 /10 matched human leukocyte antigen (HLA) identical sibling hematopoietic cell donor, unless recommendation for enrollment is provided by the Comite de Surveillance following a review of the case. • Clinically significant, active bacterial, viral, fungal, or parasitic infection. • Contraindication to anesthesia for bone marrow harvesting. • Any prior or current malignancy, myeloproliferative or immunodeficiency disorder. • A white blood cell (WBC) count < 3×10^9/L and/or platelet count < 120×10^9/L. • History of major organ damage including: o Liver disease, with transaminase levels > 3× upper limit of normal. o This observation will not be exclusionary if a liver biopsy shows no evidence of extensive bridging fibrosis, cirrhosis, or acute hepatitis. o Histopathological evidence of extensive bridging fibrosis, cirrhosis, or acute hepatitis on liver biopsy. o Heart disease, with a left ventricular ejection fraction < 25%.

	○ Kidney disease with a calculated creatinine clearance < 30% normal value. ○ Severe iron overload, which in the opinion of the physician is grounds for exclusion. ○ A cardiac T2* < 10 ms by magnetic resonance imaging (MRI). • Evidence of clinically significant pulmonary hypertension requiring medical intervention.

	HGB 206
Inclusion Criteria	• Be greater than or equal to 12 and less than or equal to 50 years of age at time of consent. • Diagnosis of sickle cell disease (SCD), with either βS/βS or βS/β0 or βS/β+ genotype. • Have severe SCD. i.e., in the setting of appropriate supportive care measures for SCD (e.g.,pain management plan) have experienced at least 4 severe VOEs in the 24 months prior to informed consent. ○ For the purposes of this study, a severe VOE is defined as an event with no medically determined cause other than a vaso-occlusion, requiring a greater than or equal to 24-hour hospital or Emergency Room (ER) observation unit visit or at least 2 visits to a day unit or ER over 72 hours with both visits requiring intravenous treatment. Exception: priapism does not require hospital admission but does require a medical facility visit; 4 priapism episodes that require a visit to a medical facility (without inpatient

		admission) are sufficient to meet criterion. • Karnofsky performance status of greater than or equal to 60 (for patients greater than or equal to 16 years of age) or a Lansky performance status of greater than or equal to 60 (for patients less than 16 years of age). • Have either experienced hydroxyurea (HU) failure at any point in the past or must have intolerance to HU (defined as patient being unable to continue to take HU per PI judgement). • Have been treated and followed for at least the past 24 months prior to Informed Consent in medical center(s) that maintained detailed records on SCD history.
	Exclusion Criteria	• Positive for presence of human immunodeficiency virus type 1 or 2 (HIV-1 and HIV-2), hepatitis B virus (HBV), or hepatitis C (HCV). • Clinically significant and active bacterial, viral, fungal, or parasitic infection. • Inadequate bone marrow function, as defined by an absolute neutrophil count of < 1000/microliter (< 500/microliter for subjects on HU treatment) or a platelet count < 100,000/microliter. • Any history of severe cerebral vasculopathy: defined by overt or hemorrhagic stroke; abnormal transcranial Doppler [greater than or equal to 200 cm/sec] needing chronic transfusion; or occlusion or stenosis in the polygon of Willis; or presence of Moyamoya disease. Subjects with radiologic evidence of silent infarction in the absence of any of the above criteria would still be eligible. • Advanced liver disease, defined as: o Persistent aspartate transaminase, alanine transaminase, or direct

		bilirubin value >3× the upper limit of normal (ULN), or ○ Baseline prothrombin time or partial thromboplastin time > 1.5× ULN, suspected of arising from liver disease, or ○ Magnetic Resonance Imaging (MRI) of the liver demonstrating clear evidence of cirrhosis, or ○ MRI findings suggestive of active hepatitis, significant fibrosis, inconclusive evidence of cirrhosis, or liver iron concentration greater than or equal to 15 mg/g require follow-up liver biopsy in subjects greater than or equal to 18 years of age. In subjects less than 18 years of age, these MRI findings are exclusionary, unless in the opinion of the Investigator, a liver biopsy could provide additional data to confirm eligibility and would be safe to perform. If a liver biopsy is performed based on MRI findings, any evidence of cirrhosis, bridging fibrosis, or significant active hepatitis will be exclusionary. • Any contraindications to the use of plerixafor during the mobilization of hematopoietic stem cells and any contraindications to the use of busulfan and any other medicinal products required during the myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients. • Any prior or current malignancy or immunodeficiency disorder,

	except previously treated, non-life threatening, cured tumors such as squamous cell carcinoma of the skin. • Prior receipt of an allogeneic transplant. • Immediate family member with a known or suspected Familial Cancer Syndrome. • Diagnosis of significant psychiatric disorder of the subject that, in the Investigator's judgment, could seriously impede the ability to participate in the study. • Pregnancy or breastfeeding in a postpartum female or absence of adequate contraception for fertile subjects. • Participation in another clinical study with an investigational drug within 30 days of Screening. • Prior receipt of gene therapy. • Patients needing curative anticoagulation therapy during the period of conditioning through platelet engraftment (patients on prophylactic doses of anticoagulants are eligible). • Unable to receive RBC transfusion.

	HGB 207 (Study 1)
Inclusion Criteria	• Participants less than or equal to 50 years of age at the time of consent or assent (as applicable), and able to provide written consent (adults, or legal guardians, as applicable) or assent (adolescents or children). Provided that the Data Monitoring Committee (DMC) has approved enrolling participants younger than 5 years of age, participants younger than 5 years of age may be enrolled if they weigh a minimum of 6 kilograms (kg) and are 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 milliliter per kilogram per year (mL/kg/year) of pRBCs in the 2 years preceding enrollment (all participants) or be managed under standard thalassemia guidelines with greater than or equal to 8 transfusions of pRBCs per year in the 2 years preceding enrollment (participants greater than or equal to 12 years). • Clinically stable and eligible to undergo (HSCT). • Treated and followed for at least the past 2 years in a specialized center that maintained detailed medical records, including transfusion history.
	Exclusion Critiera	• Presence of a mutation characterized as β0 mutation at both alleles of the β-globin gene (HBB) gene. • Positive for presence of human immunodeficiency virus type 1 or 2 (HIV-1 and HIV-2), hepatitis B virus (HBV), or hepatitis C (HCV). • A white blood cell (WBC) count less than (<) 3×10^9/Liter (L), and/or platelet count < 100×10^9/L not related to hypersplenism. • Uncorrected bleeding disorder. • Any prior or current malignancy. • Immediate family member with a known Familial Cancer Syndrome. • Prior HSCT. • Advanced liver disease. • A cardiac T2* < 10 ms by MRI. • Any other evidence of severe iron overload that, in the Investigator's opinion, warrants exclusion. • Participation in another clinical study with an investigational drug within 30 days of Screening. • Any other condition that would render the participant ineligible

	for HSCT, as determined by the attending transplant physician or investigator. • Prior receipt of gene therapy. • Pregnancy or breastfeeding in a postpartum female or absence of adequate contraception for fertile participant. • A known and available Human leukocyte antigen (HLA) matched family donor. • Any contraindications to the use of granulocyte colony stimulating factor (G-CSF) and plerixafor during the mobilization of hematopoietic stem cells and any contraindications to the use of busulfan and any other medicinal products required during the myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients.

	HGB 212 (Study 2)
Inclusion Criteria	• Participants less than or equal to (<=) 50 years of age at the time of consent or assent (as applicable), and able to provide written consent (adults, or legal guardians, as applicable) or assent (adolescents or children). Provided that the data monitoring committee (DMC) has approved enrolling participants younger than 5 years of age, participants younger than 5 years of age may be enrolled if they weigh a minimum of 6 kilograms (kg) and are 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 milliliter per kilogram per year (mL/kg/year) of pRBCs in the 2 years preceding enrollment (all

		participants) or be managed under standard thalassemia guidelines with >= 8 transfusions of pRBCs per year in the 2 years preceding enrollment (participants >=12 years). • Clinically stable and eligible to undergo HSCT. • Treated and followed for at least the past 2 years in a specialized center that maintained detailed medical records, including transfusion history.
	Exclusion Criteria	• Presence of a mutation characterized as other then β0 (e.g., β+, βE, βC) on at least one β-globin gene (HBB) allele. • Positive for presence of human immunodeficiency virus type 1 or 2 (HIV-1 and HIV-2), hepatitis B virus (HBV), or hepatitis C (HCV). • A white blood cell (WBC) count less than (<) 3×10^9/liter (L), and/or platelet count < 100×10^9/L not related to hypersplenism. • Uncorrected bleeding disorder. • Any prior or current malignancy. • Prior HSCT. • Advanced liver disease. • A cardiac T2* < 10 ms by MRI. • Any other evidence of severe iron overload that, in the investigator's opinion, warrants exclusion. • Participation in another clinical study with an investigational drug within 30 days of Screening. • Any other condition that would render the participant ineligible for HSCT, as determined by the attending transplant physician or investigator. • Prior receipt of gene therapy. • Pregnancy or breastfeeding in a postpartum female or absence of adequate contraception for fertile participant. • A known and available human leukocyte antigen (HLA) matched family donor.

		• Any contraindications to the use of granulocyte colony stimulating factor (G-CSF) and plerixafor during the mobilization of hematopoietic stem cells and any contraindications to the use of busulfan and any other medicinal products required during the myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients.
Safety	Zynteglo (betibeglogene autotemcel) has no FDA labeled contraindications for use.(1)	

REFERENCES

Number	Reference
1	Zynteglo prescribing information. Bluebird bio, Inc. November 2023.
2	Vichindky E, Levine L, et al. Standards of Care Guidelines for Thalassemia. 2012.
3	Thalassaemia International Federation. 2021 Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) 4th edition. Chapter 17. Pages 279-290.
4	Bluebird Bio. A Study Evaluating the Safety and Efficacy of the LentiGlobin BB305 Drug Product in β-Thalassemia Major Participants. ClinicalTrials.gov Identifer: NCT01745120.
5	Bluebird Bio. A Study Evaluating the Safety and Efficacy of LentiGlobin BB305 Drug Product in β-Thalassemia Major (Also Referred to as Transfusion-dependent β-Thalassemia [TDT]) and Sickle Cell Disease. ClinicalTrials.gov Identifier: NCT02151526.
6	Bluebird Bio. A Study Evaluating the Safety and Efficacy of bb111 in Severe Sickle Cell Disease. ClinicalTrials.gov Identifier: NCT02140554.
7	Bluebird Bio. A Study Evaluating the Efficacy and Safety of the Lentiglobin® BB305 Drug Product in Participants With Transfusion-Dependent β-Thalassemia, Who do Not Have a β0/β0 Genotype. ClinicalTrials.gov Identifier: NCT02906202.
8	Bluebird Bio. A Study Evaluating the Efficacy and Safety of the LentiGlobin® BB305 Drug Product in Participants With Transfusion-Dependent β-Thalassemia. ClinicalTrials.gov Identifier: NCT03207009.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
J3393	Zynteglo	betibeglogene autotemcel iv susp		M ; N ; O ; Y	N		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Zynteglo	betibeglogene autotemcel iv susp		Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient has a diagnosis of transfusion dependent Beta-thalassemia (β-thalassemia major or TDT) **AND** 2. ONE of the following: A. The patient is less than 12 years of age AND BOTH of the following: 1. If the patient is less than 5 years of age, then BOTH of the following: A. The patient weighs greater than or equal to 6 kg **AND** B. The prescriber has determined that the patient is able to provide the minimum number of cells **AND** 2. ONE of the following: A. The patient has a history of at least 100 mL/kg/year of packed red blood cells (pRBC) in the previous 12 months **OR** B. The patient has required greater than or equal to 8 pRBC transfusions in the past 12 months **OR** B. The patient is at least 12 years of age but less than or equal to 50 years of age AND ONE of the following: 1. The patient has a history of at least 100 mL/kg/year of packed red blood cells (pRBC) in the past 12 months **OR** 2. The patient has required greater than or equal to 8 pRBC transfusions in the past 12 months **AND** 3. The patient is clinically stable and able to undergo a hematopoietic stem cell transplant (HSCT) **AND** 4. The patient does NOT have a white blood cell count < 3 X 10^9/L and/or a platelet count < 100 X10^9/L **AND** 5. The patient does NOT have evidence of an uncorrected bleeding disorder **AND** 6. ONE of the following: A. The patient does NOT have any prior or current malignancy that required systemic therapy **OR** B. The patient has had adequately treated cone-biopsied in situ carcinoma of the cervix uteri **OR** C. The patient has had adequately treated basal or squamous cell carcinoma of the skin **AND** 7. The patient does NOT have advanced liver dysfunction as defined by any of the following: A. ALT (alanine transaminase) 3 times the upper limit of normal B. Bilirubin above 3 times the upper limit of normal C. Alkaline phosphatase above 3 times the upper limit of normal D. INR (international normalized ratio) greater than or equal to 1.4 **AND** 8. The patient does NOT have a T2* < 10 ms by magnetic resonance imaging (MRI) **AND** 9. The patient does NOT have severe iron overload that in the provider's opinion warrants exclusion **AND** 10. The patient is NOT HIV positive **AND** 11. BOTH of the following: A. The patient has a negative hepatitis B surface antigen (HBsAg) **AND** B. ONE of the following: 1. The patient's hepatitis B core antibody (HBcAB) is negative **OR** 2. The patient's HBcAB is positive due to a resolved hepatitis B infection AND the patient's HBV virus DNA is negative **AND** 12. ONE of the following: A. The patient’s hepatitis C virus (HCV) antibody is negative **OR** B. The patient’s HCV antibody is positive AND the patient’s HCV RNA is negative **AND** 13. The patient does NOT have another active infection **AND**

Module	Clinical Criteria for Approval
	14. The patient has NOT had previous gene therapy for the requested diagnosis **Length of Approval:** 1 course per lifetime

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

REVISIONS	
11-15-2022	Policy added to the bcbsks.com web site. Policy maintained by Prime Therapeutics LLC
03-26-2024	Policy reviewed with no updates made. Policy maintained by Prime Therapeutics LLC
07-01-2024	Added new code J3393 (eff. 07-01-2024)
10-08-2024	Policy reviewed by Prime Therapeutics with non-clinical edits