Gene therapies for sickle cell disease and beta (β) - thalassemia - Casgevy (exagamglogene autotemcel) and Lyfgenia (lovotibeglogene autotemcel)

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Related Policies

- n/a

Coverage Rationale

Sickle Cell Disease

For coverage of Casgevy (exagamglogene autotemcel) intravenous infusion for treatment of Sickle Cell Disease, all of the following will be required:

- Diagnosis of sickle cell disease with submission of medical records (e.g., chart notes) confirming patient has one of the following genotypes: β S/ β S or β S/ β 0, or β S/ β + **and**
- Patient is 2 years of age or older **and**
- Provider attests that patient is clinically stable and eligible to undergo hematopoietic stem cell transplant (HSCT) **and**
- Patient has a history of at least 4 vaso-occlusive events (VOEs) in the past 24 months as defined by one of the following scenarios:
    - Acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or intravenous [IV] non-steroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions
    - Acute chest syndrome
    - Priapism lasting > 2 hours and requiring a visit to a medical facility
    - Splenic sequestration **and**
- Patient is anticipated to provide an adequate number of cells to meet the minimum recommended dose of 3 x 10^6 CD34+ cells/kg **and**
- Patient will receive both of the following:
    - Full myeloablative conditioning with busulfan prior to treatment with Casgevy
    - Anti-seizure prophylaxis with agents other than phenytoin prior to initiating busulfan conditioning **and**
- Prescriber attests that patient will discontinue disease-modifying therapies for sickle cell disease (e.g., hydroxyurea, crizanlizumab, voxelotor) 8 weeks before the planned start of mobilization and conditioning **and**

- Both of the following:
    - Patient has never received any previous sickle cell gene therapy treatment in their lifetime (i.e., Casgevy, Lyfgenia)
    - Patient has never received prior allogeneic transplant **and**
- Prescribed by one of the following at a SCD treatment center with expertise in gene therapy and with shared decision-making regarding treatment risks:
    - Hematologist/Oncologist
    - Specialist with expertise in the diagnosis and management of sickle cell disease

Sickle Cell Disease

For coverage of Lyfgenia (lovotibeglogene autotemcel) intravenous infusion for Sickle Cell Disease, all of the following will be required:

- Diagnosis of sickle cell disease with submission of medical records (e.g., chart notes) confirming patient has one of the following genotypes: β S/ β S, β S/ β 0, or β S/ β + **and**
- Patient is 12 years of age or older **and**
- Provider attests that patient is clinically stable and eligible to undergo hematopoietic stem cell transplant (HSCT) **and**
- Patient has a history of at least 4 vaso-occlusive events (VOEs) in the past 24 months as defined by one of the following scenarios:
    - An episode of acute pain with no medically determined cause other than vaso-occlusion, lasting more than 2 hours
    - Acute chest syndrome
    - Acute hepatic sequestration
    - Acute splenic sequestration
    - VOE requiring a hospitalization or multiple visits to an emergency department/urgent care over 72 hours and receiving intravenous medications at each visit
    - Priapism requiring any level of medical attention **and**
- Submission of medical records (e.g., chart notes) confirming patient has less than or equal to two α -globin gene deletions **and**
- Patient is anticipated to provide an adequate number of cells to meet the minimum recommended dose of 3 x 10^6 CD34+ cells/kg **and**
- Patient will receive both of the following:
    - Full myeloablative conditioning with busulfan prior to treatment with Lyfgenia
    - Anti-seizure prophylaxis with agents other than phenytoin prior to initiating busulfan conditioning **and**
- Prescriber attests that patient will discontinue disease-modifying therapies for sickle cell disease (e.g., hydroxyurea, crizanlizumab, voxelotor) 8 weeks before the planned start of mobilization and conditioning **and**
- Both of the following:
    - Patient has never received any previous sickle cell gene therapy treatment in their lifetime (i.e., Casgevy, Lyfgenia)
    - Patient has never received prior allogeneic transplant **and**
- Prescribed by one of the following at a SCD treatment center with expertise in gene therapy and with shared decision-making regarding treatment risks:
    - Hematologist/Oncologist
    - Specialist with expertise in the diagnosis and management of sickle cell disease

Transfusion-dependent β -thalassemia (TDT)

For coverage of Casgevy (exagamglogene autotemcel) intravenous infusion for Transfusion-dependent β -thalassemia (TDT), the following will be required:

- Diagnosis of transfusion-dependent β -thalassemia (TDT) **and**

- Submission of medical records (e.g., chart notes) confirming presence of a mutation at both alleles of the β-globin gene (e.g. β0/β0, β0/β+, β+/β+, β0/βE) **and**
- One of the following:
  - Patient has a history of requiring at least 100 mL/kg/year of RBC transfusions in the prior 2 years **or**
  - Patient requires 10 units/year of RBC transfusions in the prior 2 years **and**
- Patient is 2 years of age or older **and**
- Provider attests that patient is clinically stable and eligible to undergo hematopoietic stem cell transplant (HSCT) **and**
- Patient is anticipated to provide an adequate number of cells to meet the minimum recommended dose of 3 x 10^6 CD34+ cells/kg **and**
- Patient does not have any of the following:
  - Severely elevated iron in the heart (e.g., patients with cardiac T2* less than 10 msec by MRI)
  - Advanced liver disease
  - MRI results of the liver demonstrating liver iron content greater than or equal to 15 mg/g (unless biopsy confirms absence of advanced disease) **and**
- Both of the following:
  - Iron chelation therapy (e.g., deferoxamine, deferasirox) will be discontinued for at least 7 days prior to initiating myeloablative conditioning therapy
  - Hydroxyurea, Oxbryta (voxelotor), and Adakveo (crizanlizumab) will be discontinued at least 8 weeks prior to start of mobilization and conditioning **and**
- Patient will receive both of the following:
  - Full myeloablative conditioning with busulfan prior to treatment with Casgevy
  - Anti-seizure prophylaxis with agents other than phenytoin prior to initiating busulfan conditioning **and**
- Both of the following:
  - Patient has never received any previous transfusion-dependent β-thalassemia gene therapy treatment in their lifetime (i.e., Casgevy, Zynteglo)
  - Patient has never received prior allogeneic transplant **and**
- Prescribed by one of the following at a treatment center with expertise in gene therapy and with shared decision-making regarding treatment risks:
  - Hematologist/Oncologist
  - Stem transplant specialist

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J3392	Injection, exagamglogene autotemcel, per treatment
J3394	Injection, lovotibeglogene autotemcel, per treatment

ICD-10 Code	Description
D56	Thalassemia
D56.1	Beta thalassemia
D56.5	Hemoglobin E-beta thalassemia

ICD-10 Code	Description
D57	Sickle-cell disorders
D57.0	Hb-SS disease with crisis
D57.00	Hb-SS disease with crisis, unspecified
D57.01	Hb-SS disease with acute chest syndrome
D57.02	Hb-SS disease with splenic sequestration
D57.03	Hb-SS disease with cerebral vascular involvement
D57.04	Hb-SS disease with dactylitis
D57.09	Hb-SS disease with crisis with other specified complication
D57.1	Sickle-cell disease without crisis
D57.2	Sickle-cell/Hb-C disease
D57.20	Sickle-cell/Hb-C disease without crisis
D57.21	Sickle-cell/Hb-C disease with crisis
D57.211	Sickle-cell/Hb-C disease with acute chest syndrome
D57.212	Sickle-cell/Hb-C disease with splenic sequestration
D57.213	Sickle-cell/Hb-C disease with cerebral vascular involvement
D57.214	Sickle-cell/Hb-C disease with dactylitis
D57.218	Sickle-cell/Hb-C disease with crisis with other specified complication
D57.219	Sickle-cell/Hb-C disease with crisis, unspecified
D57.4	Sickle-cell thalassemia
D57.40	Sickle-cell thalassemia without crisis
D57.41	Sickle-cell thalassemia, unspecified, with crisis
D57.411	Sickle-cell thalassemia, unspecified, with acute chest syndrome
D57.412	Sickle-cell thalassemia, unspecified, with splenic sequestration
D57.413	Sickle-cell thalassemia, unspecified, with cerebral vascular involvement
D57.414	Sickle-cell thalassemia, unspecified, with dactylitis
D57.418	Sickle-cell thalassemia, unspecified, with crisis with other specified complication
D57.419	Sickle-cell thalassemia, unspecified, with crisis
D57.42	Sickle-cell thalassemia beta zero without crisis
D57.43	Sickle-cell thalassemia beta zero with crisis
D57.431	Sickle-cell thalassemia beta zero with acute chest syndrome
D57.432	Sickle-cell thalassemia beta zero with splenic sequestration
D57.433	Sickle-cell thalassemia beta zero with cerebral vascular involvement
D57.434	Sickle-cell thalassemia beta zero with dactylitis
D57.438	Sickle-cell thalassemia beta zero with crisis with other specified complication
D57.439	Sickle-cell thalassemia beta zero with crisis, unspecified
D57.44	Sickle-cell thalassemia beta plus without crisis
D57.45	Sickle-cell thalassemia beta plus with crisis
D57.451	Sickle-cell thalassemia beta plus with acute chest syndrome
D57.452	Sickle-cell thalassemia beta plus with splenic sequestration

ICD-10 Code	Description
D57.453	Sickle-cell thalassemia beta plus with cerebral vascular involvement
D57.454	Sickle-cell thalassemia beta plus with dactylitis
D57.458	Sickle-cell thalassemia beta plus with crisis with other specified complication
D57.459	Sickle-cell thalassemia beta plus with crisis, unspecified
D57.8	Other sickle-cell disorders
D57.80	Other sickle-cell disorders without crisis
D57.81	Other sickle-cell disorders with crisis
D57.811	Other sickle-cell disorders with acute chest syndrome
D57.812	Other sickle-cell disorders with splenic sequestration
D57.813	Other sickle-cell disorders with cerebral vascular involvement
D57.814	Other sickle-cell disorders with dactylitis
D57.818	Other sickle-cell disorders with crisis with other specified complication
D57.819	Other sickle-cell disorders with crisis, unspecified

Background

Beta (β)-thalassemia

Beta (β)-thalassemia is an inherited blood disorder caused by a genetic mutation of the β-globin gene (HBB) that leads to reduced or absent synthesis of the β-globin proteins of hemoglobin (Hb) (the iron-containing protein component of red blood cells [RBCs]), thereby reducing the amount of functional Hb and manifesting in clinically significant anemia (Beaudoin et al 2023, National Institutes of Health [NIH] Web site 2026, National Organization for Rare Disorders [NORD] Web site 2026).

The incidence of symptomatic cases of β-thalassemia in the general population is approximately 1 in 100,000 individuals. β-thalassemia is most commonly seen in Mediterranean, Middle Eastern, African, and central Asian, Indian subcontinent, and Far East populations (NORD Web site 2026). In the United States (U.S.), the estimated number of patients with β-thalassemia is < 5000, with an estimated 1000 to 1500 patients living with transfusion-dependent β-thalassemia (TDT) (Beaudoin et al 2023, NIH Web site 2026).

Regular, lifelong RBC transfusions are the principal supportive intervention for patients with β-thalassemia major (Taher et al 2025). RBC transfusions expose the patient to a variety of risks and AEs, such as non-hemolytic febrile transfusion reactions, acute hemolytic reactions, allergic reactions, and alloantibody development, among others. RBC transfusions often lead to iron overload, which can cause organ damage and increase the risk of heart failure, endocrine system damage, liver cirrhosis, and hepatocellular carcinoma, and lead to decreased survival. Iron chelation therapy improves survival and may decrease morbidity from iron overload; however, once iron has deposited in some tissues, damage is often irreversible.

Sickle cell disease (SCD)

SCD is a rare, progressive, debilitating, genetic hematologic disorder consisting of a broad group of inherited red blood cell (RBC) disorders (hemoglobinopathies) (Centers for Disease Control and Prevention [CDC] Web site 2026, FDA exa-cel briefing document 2023, FDA Lyfgenia pharmacology-toxicology review 2023, Vichinsky 2026). SCD is caused by a single point mutation on the β-globin gene due to a substitution of the amino acid valine for glutamic acid at the sixth position of the β-globulin chain, producing an abnormal β A-globin chain, and resulting in the production of β S-globin. This mutation forms sickle hemoglobin (HbS). High concentrations of Hb with β S-globin subunits (i.e., HbS) result in polymerization within RBCs when deoxygenated, creating rigid, sticky, deformed sickle-shaped RBCs that aggregate

causing vaso-occlusion, tissue ischemia and organ damage, and hemolysis, and lead to a marked reduction in RBC lifespan. SCD encompasses different Hb genotypes, including homozygous hemoglobin SS (HbSS) and the compound heterozygous conditions, HbS β 0-thalassemia, HbS β +-thalassemia (i.e., β S/ β S, β S/ β 0, and β S/ β + genotypes), and hemoglobin sickle cell disease (HbSC) (Department of Health and Human Services [DHHS] 2014, Vichinsky 2026). HbSS and HbS β 0-thalassemia (commonly referred to as sickle cell anemia [SCA]) are clinically similar and associated with the most severe clinical manifestations of SCD (Vichinsky 2026).

SCD affects millions of people throughout the world. It is estimated that SCD affects approximately 100,000 Americans and occurs in 1 out of every 365 Black or African-American births and 1 out of every 16,300 Hispanic-American births (CDC Web site 2024). Although SCD is associated with major morbidity, currently > 90% of children with SCD in the U.S. and the United Kingdom (UK) survive into adulthood; however, their lifespans remain shortened by 2 or 3 decades compared to the general population (DHHS 2014).

Clinical Evidence

The clinical evidence supporting these therapies comes primarily from single-arm, open-label trials with clinically meaningful outcomes, including transfusion independence in TDT and freedom from severe vaso-occlusive events in SCD. Because these are one-time autologous cellular therapies requiring myeloablative conditioning, interpretation of efficacy should be balanced with transplant-related risks, long-term safety follow-up, and uncertainty regarding durability beyond the available follow-up periods.

Casgevy (exagamglogene autotemcel [exa-cel]) for Transfusion-dependent β-thalassemia (TDT)
The FDA approval of exa-cel for TDT was based on data from an ongoing 24-month, Phase 1/2/3, open-label (OL), single-arm, multi-center (MC) trial (CLIMB THAL-111) in 59 patients 12 to 35 years of age (median, 20) with TDT (Casgevy prescribing information 2026, FDA Casgevy SBRA 2024, FDA Casgevy statistical review 2024, Frangoul et al 2021, Locatelli et al 2023, Locatelli et al 2023 [poster]). The study enrolled patients with a history of RBC transfusions (≥ 100 mL/kg/year or ≥ 10 units/year in the 2 years preceding enrollment) and eligible to undergo HSCT; exclusion criteria included patients with an available 10/10 HLA-matched related hematopoietic stem cell donor and those who had undergone prior allo-HSCT. As of the data cut-off date of January 16, 2023, 52 patients were treated with exa-cel (i.e., the full analysis set [FAS] population) and 35 had sufficient follow-up of ≥ 16 months (i.e., the primary efficacy set [PES] population) to be evaluable for the primary efficacy outcome. The median total duration of follow-up post-infusion in the PES population was 23.8 months (range, 16.1 to 48.1). Treatment consisted of a single dose of exa-cel (autologous CRISPR-Cas9 modified CD34+ hHSPCs) administered via intravenous (IV) infusion (target dose of ≥ 3.0×10^6 CD34+ cells/kg; the median dose was 7.5 [range, 3.0 to 19.7] × 10^6 CD34+ cells/kg). The mean and median number of mobilization and apheresis cycles required for the collection of CD34+ cells were 1.3 (standard deviation [SD], 0.7) and 1 (range, 1 to 4), respectively. Neutrophil engraftment occurred by a median of 29 days (range, 12 to 56). There were no cases of graft failure or rejection.

- Primary endpoint: The TI12 responder rate (defined as a weighted average Hb ≥ 9 g/dL without any RBC transfusions for ≥ 12 consecutive months any time within the first 24 months after exa-cel infusion) was 32/35 (91.4%; 98.3% 1-sided confidence interval [CI], 75.7 to 100).
    - The 3 patients who did not achieve TI12 had reductions in annualized RBC transfusion volume requirements ranging from 79.8% to 97.9% compared to baseline requirements.
- Secondary endpoints:
    - The TI6 responder rate was 32/35 (91.4%; 98.3% 1-sided CI, 75.7 to 100).
    - All patients who achieved TI12 remained transfusion-independent, with a mean and median duration of transfusion-independence of 19.2 (SD, 2.8) and 20.8 (range, 13.3 to 45.1) months, respectively, and normal mean weighted average total Hb levels of 13.1 (SD, 1.4) g/dL.
    - Analyses of Hb and HbF demonstrated increases in mean total Hb, HbF levels, and HbF % for patients in the PES, which occurred early in the study and were maintained over time throughout the study.

For safety, no cases of graft failure or graft rejection, deaths, or malignancies were reported.

In a study evaluating patient-reported outcomes following exa-cel infusion in 54 CLIMB THAL-111 participants (adults, n=35; adolescents, n=19) with ≥16 months follow-up, clinically meaningful and sustained improvements in health-related quality of life (HRQOL) were observed (Fuente et al, 2025). In adults, improvements were seen in EQ-5D-5L visual analog scale (VAS) and health utility index scores, exceeding minimal clinically important differences (MCIDs) and sustained through month 48. Functional Assessment of Cancer Therapy–Bone Marrow Transplant (FACT-BMT) scores also improved, including all domains of physical, social/family, emotional, and functional well-being. Similarly, adolescents demonstrated improvements in EQ-5D-Y VAS and Pediatric Quality of Life Inventory (PedsQL) total scores at month 24, with sustained gains in both physical and psychosocial health domains.

CLIMB THAL-141 is an ongoing 24-month, Phase 3, OL, single-arm, MC study evaluating exa-cel in children 2 to 11 years of age with TDT, with results published for patients aged 5-11 (Frangoul et al 2026). Eligible patients had confirmed TDT and a history of receiving ≥ 100 mL/kg/year of packed RBC transfusions during each of the 2 years before screening. After completion of the 24-month study, patients were offered enrollment in the long-term follow-up study CLIMB-131 for up to 13 additional years. Data are from the January 16, 2026 data cut-off.

A total of 15 children with TDT received exa-cel. At baseline, 5 patients (33%) had β 0/ β 0 or β 0/ β 0-like genotypes and 10 patients (67%) had non- β 0/ β 0-like genotypes. The mean age was 7.5 years (SD, 2.2). In the 2-year period before screening, the median annualized number of RBC transfusion episodes was 13.5 per year (range, 12.0 to 17.5), and the median annualized volume of RBC transfusions was 232.3 mL/kg/year (range, 173.5 to 352.3). Most patients (93%) had an intact spleen. The median number of mobilization cycles was 1 (range, 1 to 2), and the median exa-cel dose was 11.9 x 10^6 CD34+ cells/kg (range, 3.9 x 10^6 to 18.8 x 10^6). Median follow-up after exa-cel infusion was 16.0 months (range, 2.2 to 32.1). All patients achieved neutrophil engraftment at a median of 30 days (range, 19 to 38), and all except one patient achieved platelet engraftment at a median of 51 days (range, 22 to 82); one patient died before platelet engraftment occurred.

- The primary endpoint was transfusion independence for ≥ 12 consecutive months, defined as maintaining a weighted average Hb level ≥ 9 g/dL without RBC transfusion for ≥ 12 consecutive months. Evaluation of the endpoint began 60 days after the last RBC transfusion for post-transplant support or TDT management.
    - Of the 15 children treated with exa-cel, 8 were evaluable for the primary endpoint, and all 8 (100%; 95% CI, 63 to 100) achieved transfusion independence for ≥ 12 consecutive months.
    - The remaining 7 patients were not yet evaluable.
    - Among the 8 patients who achieved transfusion independence, the mean duration of transfusion independence was 23.4 months (range, 13.3 to 28.5).
    - Patients stopped receiving RBC transfusions at a mean of 1.3 months (range, 0.5 to 2.4) after exa-cel infusion.
- Secondary and pharmacodynamic endpoints:
    - Mean total Hb was 11.9 g/dL (SD, 1.3) at Month 6, which was within the age-adjusted normal range, and was sustained at ≥ 11.6 g/dL thereafter.
    - Mean HbF concentration was 10.8 g/dL (SD, 1.7) at Month 6 and remained ≥ 10.5 g/dL thereafter.
    - HbF distribution was pan-cellular, with ≥ 99% F-cells reported after exa-cel infusion.
    - Allelic editing at the BCL11A locus was detectable in peripheral blood cells within 1 month after exa-cel infusion, with the mean percentage of edited alleles maintained at ≥ 60% from Month 3 onward. In bone marrow CD34+ cells, the mean percentage of edited BCL11A alleles was 77.4% (SD, 8.5%) at Month 6 and remained stable thereafter.

The safety profile of exa-cel in CLIMB THAL-141 was generally consistent with myeloablative busulfan conditioning and autologous HSCT. All 15 children experienced at least one AE and at least one grade 3 or grade 4 AE. Common grade ≥ 3 AEs included febrile neutropenia, stomatitis, decreased neutrophil count, thrombocytopenia, anemia, mucosal inflammation, hepatic iron overload, leukopenia, and veno-occlusive liver disease. Five children (33%) experienced

serious AEs. Two children experienced serious veno-occlusive liver disease, both considered related to busulfan conditioning and not related to exa-cel. One of these patients developed multiorgan failure and pneumonia and died on study day 132. No graft failure, cancer, or other deaths were reported.

Casgevy (exagamglogene autotemcel [exa-cel]) Sickle cell disease (SCD)
The FDA approval of exa-cel was based on unpublished interim data from the ongoing 24-month, Phase 1/2/3, OL, single-arm, MC CLIMB SCD-121 trial in patients 12 to 35 years of age (median, 20; range, 12 to 34) with severe SCD (FDA Casgevy clinical pharmacology biologic license application [BLA] review 2023, FDA Casgevy SBRA 2023, FDA Casgevy statistical review 2023, Frangoul et al 2021). As of the data cut-off date of June 14, 2023, 44 patients were treated with exa-cel (ie, FAS), with 31 having sufficient follow-up of ≥ 16 months to be included in the PES. The median duration of follow-up post exa-cel infusion in the PES was 19.3 months (range, 0.8 to 48.1). Key inclusion criteria included severe SCD with a β^S/β^S, β^S/β^0, or β^S/β^+ genotype, with ≥ 2 severe VOC (sVOC) events per year during each of the previous 2 years prior to enrollment. sVOCs were defined as: an acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or IV non-steroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions, ACS, priapism lasting > 2 hours and requiring a visit to a medical facility, and/or splenic sequestration. Key exclusion criteria included an available 10/10 HLA-matched related donor. At baseline, 77% of patients in the PES had ≤ 4.5 sVOCs/year (range, 2.0 to 9.5); baseline total Hb in the PES was 9.4 g/dL (range, 5.7 to 12.6).

- The primary endpoint was the proportion of VF12 responders (defined as patients in the PES who did not experience any sVOCs for any ≥ 12 consecutive month period within the 24-month follow-up period post exa-cel infusion).
    - The VF12 response rate was 93.5% (29/31) (1-sided 98% CI, 77.9 to 100.0), at a median duration of 22.2 months.
    - Two VF12 non-responders experienced ≥ 3 acute pain episodes with emergency room (ER) visits from Months 12.1 to 27.4 and Months 11.7 to 14.1, respectively.
- Secondary endpoints:
    - A total of 30/30 (100%; 1-sided 98% CI, 87.0 to 100.0) patients achieved the endpoint of HF12 (defined as patients in the PES who did not require hospitalization due to sVOCs for any ≥ 12 consecutive month period within the 24-month follow-up period post exa-cel infusion).
    - Pharmacodynamic parameters (total Hb, HbF, and F-cells) in the FAS:
        - Mean (SD) total Hb levels were 11.9 (1.5) g/dL at Month 3 and maintained with a mean ≥ 11.1 g/dL from Month 6 onward.
        - The mean (SD) proportion of total Hb comprised of HbF was 36.9% (9.0%) at Month 3 and was maintained at approximately ≥ 40% from Month 6 over the 24-month duration of follow-up.
        - Mean (SD) proportion of F-cells in the FAS was 20% (13%) at baseline, 71% (14%) at Month 3, 93% (13%) at Month 6, and thereafter maintained at ≥ 95% over the duration of follow-up.

Following completion of CLIMB SCD-121, patients enroll in the long-term follow-up trial CLIMB-131 for up to 15 years after exa-cel. Data are from April 10, 2025.

46 patients (12 adolescents, 34 adults [≥18years]; mean age: 21.4 years, range: 12,34) with mean 4.2 VOCs/year at baseline received exa-cel. The median number of mobilization/apheresis cycles was 2 (range, 1, 6); 92% of adolescents underwent 1-2 cycles. 42 patients completed 2 years of follow-up in CLIMB SCD-121 and enrolled in the ongoing CLIMB-131 trial. The median follow-up was 41.3 months (range, 8.9, 70.3). After exa-cel infusion, all patients engrafted neutrophils and platelets at a median of 27 days (range, 15, 40) and 35 days (range, 23, 126), respectively. 45 patients were evaluable for the primary and key secondary endpoints in CLIMB SCD-121; 41/45 (91.1%) achieved VF12 (free of severe VOCs for ≥12 consecutive months) (95% CI: 78.8%, 97.5%) and 44/45 (97.8%) achieved HF12 (free from inpatient hospitalization for severe VOCs for ≥12 consecutive months) (95% CI: 88.2%, 99.9%).

In CLIMB SCD-121 and CLIMB-131 combined, 45/45 (100%) of patients achieved VF12 and HF12 with a mean VOC-free duration of 35.3 months (range, 12.9, 67.7). All evaluable patients had durable increases in mean hemoglobin F (HbF) of

≥40% from Month 6 onward with pan-cellular distribution (˜95% RBCs expressing HbF) resulting in normal or near normal total hemoglobin (Hb) levels. Allelic editing was stable over time in both bone marrow and peripheral blood cells. Clinically meaningful improvements in hemolysis markers (lactate dehydrogenase, haptoglobin, reticulocyte count, indirect bilirubin) and quality of life (QOL) measures were observed compared to baseline and were maintained over time.

Exa-cel safety profile was consistent with myeloablative conditioning and autologous hematopoietic stem cell transplant. Efficacy and safety were consistent in adults and adolescents and across genotypes. There was one death which occurred 8.9 months after exa-cel infusion, which was previously reported, from respiratory failure due to COVID-19 infection not related to exa-cel; no malignancies occurred (Grupp et al 2025).

CLIMB SCD-151 is an ongoing 24-month, Phase 3, OL, single-arm, MC study evaluating exa-cel in children 2 to 11 years of age with severe SCD, with results published for patients aged 5-11 (Frangoul et al 2026). Eligible patients had confirmed severe SCD, defined as the occurrence of $\geq$ 2 severe VOCs per year during each of the 2 years before enrollment. Patients with a history of stroke, high risk of stroke, or HbF > 15.0% were excluded. After completion of the 24-month study, patients were offered enrollment in the long-term follow-up study CLIMB-131 for up to 13 additional years. Data are from the January 16, 2026 data cut-off.

A total of 11 children with SCD received exa-cel, all of whom had the β^S/β^S genotype. The mean age was 8.5 years (SD, 2.6). At baseline, the mean annualized number of severe VOCs during the 2 years before screening was 3.2 (range, 2.0 to 5.0), and the mean annualized number of inpatient hospitalizations for severe VOCs was 2.7 (range, 1.0 to 5.0), with a mean annualized hospitalization duration of 17.5 days (range, 6.5 to 30.5). The median number of mobilization cycles was 2 (range, 1 to 3), and the median exa-cel dose was 5.4 x 10^6 CD34+ cells/kg (range, 3.0 x 10^6 to 8.3 x 10^6). Median follow-up after exa-cel infusion was 16.9 months (range, 7.6 to 33.1). All patients achieved neutrophil and platelet engraftment at a median of 28 days (range, 20 to 37) and 47 days (range, 24 to 78), respectively.

- The primary endpoint was freedom from severe VOCs for $\geq$ 12 consecutive months after exa-cel infusion.
    - No VOCs were observed in any of the 11 children after exa-cel infusion.
    - Of the 8 patients evaluable for the primary endpoint, all 8 (100%; 95% CI, 63 to 100) were free from severe VOCs for $\geq$ 12 consecutive months.
    - The remaining 3 patients were not yet evaluable. Among the 8 evaluable patients, the mean duration of freedom from VOCs was 19.0 months (range, 13.2 to 30.1).

- Secondary endpoints:
    - All 8 evaluable patients achieved HF12.
    - The median time from exa-cel infusion to the last RBC transfusion was 1.1 months (range, 0.5 to 2.1).
    - Mean total hemoglobin was 11.8 g/dL (SD, 1.1) at Month 3 and 12.2 g/dL (SD, 1.4) at Month 6, and was maintained within the normal age-adjusted hemoglobin range thereafter.
    - Mean HbF was 38.1% (SD, 8.3%) at Month 3 and 49.5% (SD, 6.4%) at Month 6, and remained > 45% thereafter.
    - HbF distribution was pan-cellular, with mean F-cells exceeding 98% from Month 6 onward.
    - Allelic editing at the BCL11A locus was stable over time. Mean edited alleles in peripheral blood were 67.9% (SD, 7.3%) at Month 3 and remained > 66% thereafter; in bone marrow CD34+ cells, mean edited alleles were 84.5% (SD, 4.9%) at Month 6 and remained stable thereafter.

The safety profile of exa-cel in CLIMB SCD-151 was consistent with myeloablative busulfan conditioning and autologous HSCT. All 11 children experienced at least one AE and at least one grade 3 or grade 4 AE. Common grade $\geq$ 3 AEs included febrile neutropenia, mucosal inflammation, decreased platelet count, anemia, decreased neutrophil count, thrombocytopenia, leukopenia, and neutropenia. Five children (45%) experienced serious AEs; none occurred in more than one patient and none were considered related to exa-cel by the investigator. No deaths, graft failure, cancer, or AEs leading to study discontinuation were reported in children with SCD.

Lyfgenia (lovotibeglogene autotemcel [lovo-cel]) for Sickle cell disease (SCD)
The FDA approval of lovo-cel for SCD was based on unpublished interim data from the ongoing 24-month, Phase 1/2, OL, single-arm, MC HGB-206 trial (Group C) in patients 12 to 50 years of age (median, 24; range, 12 to 38) with severe SCD (FDA Lyfgenia statistical review 2023, Kanter et al 2022). Group C included patients who were treated with lovo-cel manufactured from plerixafor-mobilized cells using the current manufacturing process. As of the data cut-off date of February 13, 2023, 36 patients in Group C (ie, transplant population [TP]) completed the parent study, with 33 enrolled into the 13-year LTFU study, with a median duration of follow-up of 38 months (range, 12 to 61) post-lovo-cel infusion. Key inclusion criteria included severe SCD with a β^S/β^S, β^S/β^0, or β^S/β^+ genotype, with ≥ 4 severe VOEs (sVOEs) in the 24 months before enrollment. sVOEs were defined as an episode of acute pain (due to a VOE), ACS, acute splenic or hepatic sequestration, and/or acute priapism requiring a ≥ 24-hour hospital/ER visit, or ≥ 2 visits to a day unit/ER over 72 hours (with exception of priapism). Key exclusion criteria included an available 10/10 HLA-matched related donor. At baseline, the median annualized number of sVOEs in the 24 months prior to informed consent was 3.0 (range, 0.0 to 16.0); baseline total Hb was 8.5 g/dL.

- The primary endpoint was the complete resolution of VOEs (VOE-CR) between 6 and 18 months post lovo-cel infusion in the transplant population for VOE (TPVOE) (n = 32). Compared with an sVOE, a VOE was defined as an event (ie, vaso-occlusive pain episode, ACS, acute hepatic sequestration, acute splenic sequestration, and/or acute priapism) requiring evaluation at a medical facility, with or without hospitalization.
    - A total of 28/32 (87.5%) patients in the TPVOE achieved VOE-CR (2-sided 95% CI, 71.0 to 96.5).
        - Additionally, between 6 and 24 months after lovo-cel infusion, 27/32 (84.4%) patients met the endpoint of VOE-CR (2-sided 95% CI, 67.2 to 94.7). Between 18 and 24 months, 1 patient died due to an event of sudden death (considered to be unlikely related to lovo-cel) and was considered as a non-responder.
- Secondary endpoints:
    - A total of 30/32 (93.8%) patients in the TPVOE achieved complete resolution of sVOEs (sVOE-CR) between 6 and 18 months post lovo-cel infusion (2-sided 95% CI, 79.2 to 99.2).
        - Additionally, between 6 and 24 months after lovo-cel infusion, 29/32 (90.6%) patients met the endpoint of sVOE-CR (2-sided 95% CI, 75.0 to 98.0).
    - A total of 31/36 (86.1%) patients in the TP met the Globin Response endpoint (2-sided 95% CI, 70.5 to 95.3).
        - Globin Response was defined as meeting the following criteria for a continuous period of ≥ 6 months post lovo-cel infusion: Weighted average HbA^{T87Q} percentage of non-transfused total Hb ≥ 30% AND weighted average non-transfused total Hb increase of ≥ 3 g/dL compared to baseline total Hb OR weighted average non-transfused total Hb ≥ 10 g/dL in the TP.
        - After the primary evaluation period to last follow-up, 4/32 (12.5%) patients who achieved VOE-CR experienced VOEs while maintaining Globin Response. After the primary evaluation period up to 24 months, 17/35 (49%) patients were prescribed opioids for sickle cell and non-sickle cell-related pain.

After 24 months of follow-up post lovo-cel infusion, patients enrolled in the long-term study LTF-307. An analysis was undertaken of 47 patients (male, 59.6%; median [range] age, 23 y [12-38]) who received a lovo-cel infusion as of Feb 13, 2023. Median (range) follow-up was 35.5 months (0.3-61.0). Median (range) time to neutrophil and platelet engraftment was 20 days (12-35) and 35 days (19-136). Peripheral blood vector copy number remained stable (median >1 c/dg through follow-up). Median HbAT87Q levels were 4.5g/dL from 6 months post infusion to last study visit. Median (range) total Hb level increased from 8.7g/dL (6.1-12.5) at relative baseline to 11.8g/dL (8.4-15.0) at last visit; median percent HbAT87Q of non-transfused total Hb was 40% or more.

Of 34 evaluable patients (ie, 18 months follow-up and 4 VOEs in the 2 years before enrollment), 30 (88.2%) and 32 (94.1%) had complete resolution of VOEs and severe VOEs during the 6-18 months post infusion, vs a median (range) of 3.5 (1.5-16.5) and 3.0 (0.5-13.0) events/year in the 2 years before enrollment.

Among patients who had globin response or who had 18 months follow-up (n=38), 33 (86.8%) achieved globin response. Hemolysis markers (eg, reticulocytes, total bilirubin, lactate dehydrogenase) approached normal levels.

Among all 47 patients, 44 (93.6%) had 1 AE of grade 3 after lovo-cel infusion; the most common of which were stomatitis (33 [70.2%] patients) and thrombocytopenia (28 [59.6%]). Serious AEs were reported for 26 (55.3%) patients, the most common of which was chronic pain/acute exacerbation of chronic pain (3 [6.4%]; 2 chronic neuropathic pain and 1 chronic pain associated with anxiety). One patient with-α3.7/-α3.7 genotype diagnosed with myelodysplastic syndrome had stable complete blood counts 30 months post infusion. No veno-occlusive liver disease, graft failure, replication-competent lentivirus, or vector-mediated insertional oncogenesis was observed. Lovo-cel treatment regimen largely reflected known side effects of HSPC collection and busulfan conditioning regimen. A total of 25 patients had evaluable HRQOL data. Mean scores for PROMIS-57 domains of pain intensity, pain interference, and fatigue improved (ie, decreased) over time up to 48 months. (Kanter et al 2024)

Place in Therapy

B-thalassemia

Regular, lifelong RBC transfusions are the principal supportive intervention for patients with β-thalassemia major (Taher et al 2025). Reblozyl (luspatercept) is another option for the treatment of *β*-thalassemia; it can be considered for patients ≥ 18 years of age who require regular RBC transfusions to achieve transfusion burden reduction (Taher et al 2025).

Allogeneic HSCT has been the first therapeutic option for curing transfusion-dependent β-thalassemia. HSCT should be offered to patients with β-thalassemia, before complications due to iron overload have developed, if an HLA identical sibling is available). A matched unrelated donor can be used if high compatibility criteria for both HLA class I and II loci are met. Availability of HSCT is often limited, however, by its availability only to young patients with a well-matched donor and the requirement for long-term immunosuppression to prevent or treat transplant-related immunological complications such GVHD and rejection, which carry a non-negligible risk of mortality (Taher et al 2025).

Gene therapy provides a new treatment option with the goal of curing β-thalassemia through the manipulation of the genome of HSCs to compensate for the inadequate or faulty function of mutated genes. For patients aged 14 years and older or for those who do not have an HLA-identical family donor, gene therapy instead constitutes an optimal therapeutic option. There are no absolute indicators from the beti-cel and exa-cel registrational studies to determine which patients should be prioritized for treatment with either one of the two products. Findings did not reveal any specific clinical characteristics associated with an improved safety and efficacy profile. Results were comparable between adolescent and adult subjects, with no observed differences in outcomes based on iron overload status, genotype, transfusion burden, or other factors. In addition, the unique challenges posed by autologous gene therapy approaches require new frameworks that cannot be directly extrapolated from the experiences and knowledge gained through allogeneic transplantation. Initial selection of patients for gene therapy treatment should be guided by the primary inclusion/exclusion criteria used in the Northstar and CLIMB THAL-111 studies (Taher et al 2025).

SCD

The 2014 NIH-sponsored, evidence-based expert consensus guidelines for SCD strongly recommended both hydroxyurea and transfusion therapy for many patients with SCD (DHHS 2014, Yawn et al 2014). Use of hydroxyurea is strongly recommended in adults with SCA with ≥ 3 sickle cell-associated moderate to severe pain crises in a 12-month period, sickle cell-associated pain that interferes with daily activities and QOL, history of severe and/or recurrent ACS, and severe symptomatic chronic anemia that interferes with daily activities and QOL. Hydroxyurea should be offered to patients ≥ 9 months of age regardless of clinical severity to reduce SCD-related complications. NIH guidelines do not address the use of L-glutamine, crizanlizumab-tmca, voxelotor, or gene therapy and briefly mention HSCT as a hope for a cure for SCD.

The American Society of Hematology (ASH) provides guidance on HSCT among other complications in SCD (Brandow et al 2020, Chou et al 2020, DeBaun et al 2020, Kanter et al 2021, Liem et al 2019). ASH 2021 guidelines state that HSCT is currently the only curative intervention for SCD, with the following recommendations:

- Related matched allo-HSCT is suggested over standard of care in patients with SCD with frequent pain, those with recurrent episodes of ACS, or those who have experienced an overt stroke or have an abnormal transcranial Doppler ultrasound (TCD).
- Allo-HSCT is suggested at an earlier rather than an older age, and use of HLA-identical sibling cord blood should be used when available and is suggested over bone marrow.

In early 2026, the American Society for Transplantation and Cellular Therapy (ASTCT) and International Society for Cell & Gene Therapy (ISCT) jointly issued practice recommendations for SCD gene therapy (Sharma et al 2026). These guidelines provide a framework for patient selection and management now that exa-cel and lovo-cel are available. They emphasize multidisciplinary evaluation and holistic patient readiness. These recommendations effectively position gene therapy as a potentially curative alternative to allo-HSCT but available to patients without matched donors. They caution that current evidence supports gene therapy in carefully chosen patients-particularly those 12–45 years old with severe SCD (frequent VOCs or organ-threatening complications) who lack an HLA-matched sibling donor and are healthy enough for transplant conditioning. The ASTCT/ISCT document underscores that gene therapy is not yet broadly accessible or tested in very young or older patients, so early adopters should mirror trial eligibility criteria (e.g. ≥2 serious VOCs/year, adequate organ reserve). It also highlights the need for informed, shared decision-making, acknowledging that gene therapy's long-term risks and durability are still being defined.

A joint European Hematology Association (EHA)– European Blood & Marrow Transplant (EBMT) panel published consensus recommendations in 2025 on selecting SCD patients for gene addition or gene editing therapy (de Franceschi et al 2025). This European expert group similarly advocates a cautious, priority-based approach during the initial rollout: gene therapy should be offered at a specialist center to patients over 12 years of age, with severe SCD (≥2 serious VOCs in previous 2 years, ≥2 ACS in the prior 2 years) who are in relatively good clinical condition and have no HLA-matched family donor. This ensures those likely to derive the greatest benefit with least risk are treated first, given the high costs, limited manufacturing capacity, and need for long-term safety data

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Casgevy (exagamglogene autotemcel) is an autologous genome edited hematopoietic stem cell-based gene therapy indicated for the treatment of patients aged 2 years and older with:

- Sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs)
- Transfusion-dependent β-thalassemia (TDT)

Lyfgenia (lovotibeglogene autotemcel) is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events.

Limitations of Use
Following treatment with LYFGENIA, patients with α-thalassemia trait (-α3.7/-α3.7) may experience anemia with erythroid dysplasia that may require chronic red blood cell transfusions. LYFGENIA has not been studied in patients with more than two α-globin gene deletions.

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Policy History/Revision Information

Date	Summary of Changes
8/21/2025	Approved by OptumRx P&T Committee
8/20/2026	Annual Review. Updated SCD and TDT Coverage Criteria to require submission of medical records for genetic testing, removed "absence of an appropriate donor" as reason patient is ineligible for a HSCT, removed requirement for negative HBV/HCV/HIV test result prior to cell collection, revised specialist criteria to include requirement for shared decision-making. Updated Casgevy to allow for use for ages 2 and up due to expanded indication. Updated SCD Coverage to include details of pre-HSCT conditioning and seizure prophylaxis. Updated Clinical Evidence and Place in Therapy sections to include recent studies, guidelines, consensus statements. Updated references.

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Archived Policy Versions (Internal Only)

Effective Date	Policy Number	Policy Title
mm/dd/yyyy – mm/dd/yyyy	######	Title of Policy Hyperlinked to KL or Other Internal Location

Nondiscrimination & Language Access Policy

Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:
Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If *you* believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

Hindi: _यान द_: य_द आप ि हंदी बोलते ह_ तो आपके ि लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_।1-800-332-6501 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-800-332-6501 (TTY: 711).

Korean: 주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다.1-800-332-6501 (TTY: 711)번으로 전화해 주십시오.

Polish: UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer1-800-332-6501 (TTY: 711).

Russian: ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода.Звоните 1-800-332-6501 (телетайп: 711).

Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al1-800-332-6501 (TTY: 711).

Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1-800-332-6501 (TTY: 711).

Traditional Chinese: 注意：如果您使用繁體中文， 您可以免費獲得語言援助服務。請 致電 1-800-332-6501 (TTY: 711)

Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-800-332-6501 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzscht, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1-800-332-6501 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1-800-332-6501 (TTY: 711).