Optum

Gene Therapy

Clinical Guideline

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Introduction

The term “gene therapy” usually has been used to describe an ex vivo or in vivo therapy whereby RNA or DNA are introduced into target cells (ex vivo) or tissues (in vivo) by a delivery vector while “cellular therapy” is a broad term that encompasses both the infusion of a cellular product for the purpose of hematopoietic reconstitution and the infusion of a cellular product intended to have a direct immunologic impact (Sharma et al., 2022). There is a general consensus among the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the American Society of Gene and Cell Therapy (ASGCT) defining gene therapy as changes in gene expression, achieved by replacing or correcting a disease-causing gene, inactivating a target gene, or inserting a new or modified gene, using a vector or delivery system of genetic sequence or gene, genetically modified microorganisms, viruses, or cells (EMA, 2020; FDA, 2018; ASGCT, 2021). The rapid growth of cellular and gene therapies over the past few years has revealed the need for an accurate and uniform taxonomy. Work is ongoing across a number of industry stakeholders including clinicians, scientists, payers, and coders to standardize nomenclature regarding what constitutes a cellular therapy or a gene therapy (Sharma et al., 2022). In the United States, the FDA establishes the regulatory framework for clinical trials and approval of therapeutic agents such as gene and cellular therapy. Specifically, the FDA Center for Biologics Evaluation and Research regulates cellular therapy products and human gene therapy products as biologics, as well as some devices related to cellular and gene therapy (FDA, 2018).

FDA approvals

Atidarsagene autotemcel (Lenmeldy™) is an autologous hematopoietic stem cell-based gene therapy approved by the FDA on March 18, 2024, for the treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ), or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy.

Betibeglogene autotemcel (Zynteglo®) is an autologous hematopoietic stem cell-based gene therapy that received FDA-approval August 17, 2022, for the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell (RBC) transfusions.

Elivaldogene autotemcel (Skysona®) was approved by the FDA on September 16, 2022, as the first gene therapy to treat boys 4 – 17 years of age with early, active cerebral adrenoleukodystrophy (CALD). The indication is approved under accelerated approval. Continued approval for this indication is contingent upon verification and description of clinical benefit in a confirmatory trial. On August 7, 2025, the FDA updated Skysona’s indication allowing it to be used only in patients without an available human leukocyte antigen (HLA)-matched donor for stem cell transplant due to concerns of an increased risk of hematologic malignancies including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).

Exagamglogene autotemcel (Casgevy™) is an autologous genome edited hematopoietic stem cell-based gene therapy indicated for treatment of sickle cell disease in patients 12 years and older with recurrent vaso-occlusive crises. Casgevy received FDA approval for this indication on December 8, 2023.

Exagamglogene autotemcel (Casgevy™) received FDA approval on January 16, 2024, for treatment of transfusion-dependent beta thalassemia in patients 12 years and older.

Lovotibeglogene autotemcel (Lyfgenia™) is an autologous hematopoietic stem-cell based gene therapy approved by the FDA on December 8, 2023, for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events. Lyfgenia carries a boxed warning for hematologic malignancy.

Prademagene Zamikeracel (Zevaskyn™) is an autologous cell sheet-based cutaneous gene therapy indicated for the treatment of wounds in adult and pediatric patients with recessive dystrophic epidermolysis bullosa (RDEB). Zevaskyn received FDA approval for this indication on April 29, 2025.

Waskyra (etuvetidigene autotemcel) is the first cell-based gene therapy for the treatment of Wiskott-Aldrich syndrome (WAS) approved by the FDA on December 9, 2025. Waskyra is indicated for pediatric patients six months and older and adults with WAS who have a mutation in the *WAS* gene and for whom hematopoietic stem cell transplantation (HSCT) is appropriate and no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

Indications

Beta thalassemia

Thalassemias are a class of disorders caused by imbalance to the alpha (α) and beta (β) globin chains that make up the principal adult oxygen transporter hemoglobin A (α_2 β_2). Beta thalassemias result from an excess of α chains due to a reduced production of β globin chains and in some instances, increased dosage of α globin genes (Mettananda et al., 2018). The beta thalassemia phenotype is determined by the degree of the imbalance and ranges from minimal effects in beta thalassemia trait to severe transfusion-dependent anemia. Complications are numerous and include growth failure, bone disease, cardiac abnormalities (pulmonary hypertension, heart failure, arrythmias), predisposition to thrombosis, extramedullary hematopoiesis (splenomegaly, masses with compression), and a broad range of endocrinopathies (Ali et al., 2021). Traditionally, beta thalassemia has been more common in certain regions of the world such as the Mediterranean, Middle East, and Southeast Asia. However, the prevalence is increasing in other regions, including Northern Europe and North America, primarily due to migration. According to the National Organization for Rare Disorders (NORD), the incidence of symptomatic cases in the United States is estimated to be approximately 1 in 100,000 individuals in the general population; males and females are equally affected. In many states, infants are diagnosed with a hemoglobin disorder through newborn screening. Each state's newborn screening program and the specific disorders tested for is different. Most states do not routinely test for thalassemia (NORD, 2018).

Beta thalassemias have been classified as thalassemia major, thalassemia intermedia, and thalassemia minor (trait), but a more useful classification is one of transfusion-dependent thalassemia (TDT) or non-transfusion-dependent thalassemia (NTDT) (Khandros & Kwiatkowski, 2019). The decision to initiate regular transfusions includes objective laboratory data as well as clinical findings and attempts to balance consequences from anemia and ineffective erythropoiesis against complications of chronic transfusion therapy. Early access to specialty care is essential so that the decision to commence transfusion can be made at the appropriate time to support normal growth and development (Lal et al., 2021). The goals of regular transfusion therapy are relief of anemia symptoms (allowing for normal growth) as well as suppression of endogenous ineffective erythropoiesis. This generally is accomplished by administering transfusions every 3 to 5 weeks to maintain hemoglobin level greater than 9.5 g/dL before transfusion. As beta thalassemia is characterized by abnormal iron metabolism resulting in increased iron absorption, monitoring and management of iron overload is an essential part of treatment. Patients with TDT are at greater risk of rapid iron loading because of the high content of iron within transfused cells. Iron deposits in the liver, heart, and endocrine glands cause significant morbidity. Iron chelation therapy is administered with the goal of reducing the toxic effects of iron overload (Khandros & Kwiatkowski, 2019). Three iron chelators are approved for use in the United States: deferoxamine, deferasirox, and deferiprone.

Allogeneic hematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen (HLA)-matched sibling donor (MSD), performed in childhood, has been the gold standard treatment for TDT for decades with probabilities of overall and thalassemia-free survival exceeding 90% and 85%, respectively. Unfortunately, siblings are available only for the minority of patients leaving fully matched unrelated donors (MUD) as the second option with similar results in terms of survival (Oikonomopoulou & Goussetis, 2021; Strocchio & Locatelli, 2018).

Treatments

Gene therapy is a novel and potentially curative treatment strategy for TDT patients that has been designed to correct the underlying α/β-globin chain ratio, thus improving the production of functional Hb, the erythropoiesis, and the chronic anemia. After isolating hematopoietic stem and progenitor cells (HSPCs), exogenous β-globin genes are incorporated into the host-cell genome using a self-activating vector. After full or partial myeloablative busulfan conditioning, these genetically modified autologous HSPCs are returned to the patient where they replicate and repopulate in the blood compartment and facilitate normal Hb synthesis. Lentiviral vectors have the ability to transfer complex genetic structures into quiescent hematopoietic stem cells. For gene therapy to be successful in beta thalassemia, certain conditions must be met: high-efficiency HSC engraftment and gene transfer, high expression of the β/γ-globin gene and appropriate expression, with minimal or no risk of insertional mutagenesis (Bou-Fakhredin et al., 2022).

Betibeglogene autotemcel (Zynteglo®) was studied in two nonrandomized, open-label, single dose phase I/II studies (HGB-204, NCT01745120 and HGB-205, NCT02151526) initiated in 2013 and enrolling 22 patients (12 – 35 years of age) with transfusion-dependent beta thalassemia. Transfusion dependence was defined as the receipt of at least eight transfusions or at least 100 ml per kilogram of body weight of packed red cells per year in the 2 years before enrollment. Patients with advanced organ damage were not eligible. Mobilized autologous CD34+ cells were obtained and transduced ex vivo with LentiGlobin BB305 vector. The cells were reinfused after the patients had undergone myeloablative busulfan conditioning. At a median of 26 months (range, 15 – 42) after infusion of the gene-modified cells, all but 1 of the 13 patients who had a non-β^0/ β^0 genotype had stopped receiving red-cell transfusions. Correction of biologic markers of dyserythropoiesis were achieved in evaluated patients with hemoglobin levels near normal ranges. In 9 patients with a β^0/β^0 genotype or two copies of the IVS1-110 mutation, the median annualized transfusion volume was decreased by 73%, and red-cell transfusions were discontinued in 3 patients. Treatment-related adverse events were typical of those associated with autologous HSCT. Grade 3 or higher adverse events occurring in two or more patients included but were not limited to stomatitis (n=12), febrile neutropenia (n=10), and veno-occlusive liver disease (n=2); the veno-occlusive liver disease was attributed to busulfan conditioning (Thompson et al., 2018).

After intravenous infusion of the thawed LentiGlobin drug product, neutrophil engraftment occurred within a median of 18.5 days (range, 14.0 – 30.0) in HGB-204 and 16.5 days (range, 14.0 – 29.0) in HBG-25. Platelet engraftment occurred within a median of 39.5 days (range, 19.0 – 191.0) in HBG-204 and 23.0 days (range, 20.0 – 26.0) in HGB-205, during which time there were no bleeding complications resulting in serious adverse events (Thompson et al., 2018).

Locatelli et al. (2022) report on an interim analysis of an open-label, phase III study (HGB-207, NCT02906202 [Northstar-2]) using beti-cel that was manufactured with a refined process. In HGB-205 and HGB-206, 11 of 14 patients with beta thalassemia and a non-β^0/ β^0 genotype had transfusion independence after infusion of beti-cel. In these patients, however, the weighted average hemoglobin levels after infusion, which ranged from 9.1 – 13.2 g/dL, were often lower than normal levels. The vector copy number and the percentage of lentiviral vector-positive cells in beti-cel were shown to be associated with hemoglobin levels; therefore, the transduction process was refined to increase the vector copy number in beti-cel and, consequently, to increase the levels of gene therapy-derived adult hemoglobin (HbA) with a T87Q amino acid substitution (HbA^{T87Q}). The primary endpoint of this study was transfusion independence defined as a weighted average hemoglobin level of at least 9 g/dL starting 60 days after the last transfusion in patients who had not received red-cell transfusions for 12 months or longer.

A total of 23 patients were enrolled and received treatment, with a median follow-up of 29.5 months. Transfusion independence occurred in 20 of 22 patients who could be evaluated (91%), including 6 of 7 patients (86%) who were younger than 12 years of age. Transfusion independence was durable; the median duration was 20.4 months (range, 15.7 – 21.6). The two evaluable patients who did not have transfusion independence had 67.4% and 22.7% reductions in transfusion volume from 6 months to the last follow-up (at 48.2 and 27.2 months, respectively). The average hemoglobin level during transfusion independence was 11.7 g/dL (range, 9.5 – 12.8). Twelve months after infusion, the median level of gene therapy-derived HbA with a T87Q amino acid substitution (HbA^{T87Q}) was 8.7 g/dL(range, 5.2 – 10.6) in patients who achieved transfusion independence. Neutrophil engraftment occurred at a

median of 23 days (range, 13 – 32) after beti-cel infusion. Neither primary nor secondary graft failure occurred. Platelet engraftment occurred at a median of 46 days (range, 20 – 94) after beti-cel infusion. A more rapid trend toward neutrophil and platelet recovery was noted in patients who had undergone splenectomy than in those with an intact spleen, even without splenomegaly or hypersplenism. Grade 3 or higher adverse events occurring in two or more patients included, but were not limited to, thrombocytopenia (n=22), neutropenia (n=18), anemia (n=14), and stomatitis (n=14). The median duration of hospitalization from conditioning through discharge was 45 days (range, 30 – 90). Additional follow-up will more fully characterize the long-term efficacy and safety of bet-cel (Locatelli et al., 2022).

Betibeglogene autotemcel (Zynteglo®) is considered medically necessary as a one-time single dose for the treatment of adult and pediatric patients with transfusion-dependent β-thalassemia when all of the following are met:

- Transfusion dependence is defined as a minimum of at least 100 mL/kg/year or 8 units/year of PRB transfusions in the most recent two years.
- Documentation of one of the following genotypes confirmed by DNA analysis (beta-globin gene [HBB] sequencing):
  - Non-β^0/β^0 (Examples: $\beta^0/\beta+$, $\beta E/\beta^0$, and $\beta+/\beta+$)
  - β^0/β^0 (Examples: $\beta^0/\beta+$ [IVS-I-110] and $\beta+$ [IVS-I-110]/$\beta+$ [IVS-I-110])
- Documentation that patient is a candidate for an allogeneic HSCT, but ineligible due to absence of an appropriate donor prior to mobilization, apheresis, and myeloablative conditioning are initiated.
- 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.
- Documentation of screening for hepatitis B virus (HBV), hepatitis C virus (HCV), human T-lymphotropic virus 1 & 2 (HTLV-1/HTLV-2), and human immunodeficiency virus 1 & 2 (HIV-1/HIV-2) prior to collection of cells for manufacturing.
- Documentation that abnormal liver function has been evaluated by hepatology.
- Documentation of an assessment of iron overload and T2* weighted MRI assessment of myocardial iron. A treatment plan must be in place if there is evidence of iron overload.
- Patients with a known prior or current malignancy must undergo oncology evaluation. Oncology clearance must include an assessment indicating the malignancy will not have any anticipated effect on survival.
- Patient has not previously received gene therapy for the requested diagnosis.
- Member is 4 years of age or older and weighs at least 6 kg; and is reasonably anticipated to provide at least the minimum number of cells required to initiate the manufacturing process.

Exagamglogene autotemcel (Casgevy™) is a cellular gene therapy consisting of autologous CD34+ hematopoietic stem cells edited by clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 technology at the erythroid specific enhancer region of the *BCL11A* gene to reduce BCL11A expression in erythroid lineage cells, leading to increased fetal hemoglobin (HbF) protein production. The autologous cells are enriched for CD34+ cells, and then genome edited *ex vivo* by introducing the CRISPR/Cas9 ribonucleoprotein (RNP) complex by electroporation. The edited cells are formulated into a suspension and administered as a hematopoietic stem cell transplant. Following infusion, the edited CD34+ cells engraft in the bone marrow and differentiate to erythroid lineage cells with reduced BCL11A expression leading to an increase in γ-globin expression and HbF protein production in erythroid cell (CRISPR Therapeutics, 2024). In patients with TDT, Casgevy has been shown to reduce or eliminate transfusion requirements.

Safety and efficacy of Casgevy in adult and adolescent patients with transfusion-dependent Beta-thalassemia was evaluated in an ongoing open-label, multi-center, single-arm trial (NCT03655678) that followed the patient for 24 months after Casgevy infusion. Those completing or discontinuing the trial were encouraged to enroll in NCT04208529, an ongoing long-term follow-up for a total of 15 years after Casgevy infusion.

Eligible patients must have had a history of requiring at least 100mL/kg/year or 10 units per year of RBC transfusions in the 2 years prior to enrollment.

At the time of interim analysis, a total of 59 patients had enrolled in the trial and 100% had started mobilization. A total of 52 (88%) patients received Casgevy infusion and formed the full analysis set (FAS). Thirty-five patients from the FAS (67%) had sufficient follow-up to allow evaluation of the primary efficacy endpoint. The median (min, max) total duration of follow-up was 23.8 (16.1, 48.1) months from the time of Casgevy infusion. There were no cases of graft failure or graft rejection.

The primary outcome was the proportion of patients achieving transfusion independence for 12 consecutive months, defined as maintaining weighted average Hb ≥ 9 g/dL without RBC transfusions for at least 12 consecutive months any time within the first 24 months after Casgevy infusion in NCT03655678, evaluated beginning 60 days after the last RBC transfusion for post-transplant support or TDT disease management. Thirty-two (91.4%) of the thirty-five patients evaluated achieved the primary outcome with a median (min, max) duration of transfusion-independence of 20.8 (13.3, 45.1) months and normal mean weighted average total Hb levels (mean [SD] 13.1 [1.4] g/dL). The median (min, max) time to last RBC transfusion was 30 (11, 91) days following Casgevy infusion. Three patients did not achieve the primary endpoint but did experience reductions in annualized RBC transfusion volume requirements of 79.8%, 83.9% and 97.9%, and reductions in annualized transfusion frequency of 78.6%, 67.4% and 94.6%, respectively, compared to baseline requirements (FDA, 2024).

Exagamglogene autotemcel (Casgevy™) is considered medically necessary as a one-time single dose for the treatment of patients aged 12 years and older with transfusion-dependent β-thalassemia when all of the following are met:

- Transfusion dependence is defined as a minimum of at least 100 mL/kg/year or 10 units/year of RBC transfusions in the most recent two years.
- Documentation of one of the following genotypes confirmed by DNA analysis (beta-globin gene [HBB] sequencing):
  - β^0/β^0 – like (β^0/β^0, β^0/IVS-I-110, and IVS-I-110/IVS-I-110 β+/β+)
  - Non-β^0/β^0 – like
- Documentation that the patient is a candidate for an allogeneic HSCT, but ineligible due to absence of an appropriate donor prior to mobilization, apheresis, and myeloablative conditioning initiation.
- Prior to apheresis it is recommended that patients be transfused with a goal to maintain Hb ≥ 11 g/dL.
- Documentation of confirmative screening shows that the patient does not have any of the following infectious diseases:
  - HIV-1
  - HIV-2
  - HBV
  - HCV
- Patient has not previously received gene therapy for the requested diagnosis.
- Patient has not previously received an allogeneic or autologous HSCT.

Cerebral adrenoleukodystrophy

Adrenoleukodystrophy (ALD) is an X-linked disorder caused by pathogenic variants within the *ABCD*1 gene, which encodes for a peroxisomal membrane protein responsible for transportation of very long-chain fatty acids (VLCFA) into the peroxisome, where they are subsequently degraded via β- oxidation. The incidence of ALD is 1 in 14,000 to17,000 births (Gupta et al., 2022). The severity of the disease is much more prominent in males, although the majority of affected women show symptoms in adulthood related to spinal cord involvement (Huffnagel et al., 2019). In males, there are three primary presentations associated with ALD; adrenal insufficiency (AI), cerebral inflammatory demyelination, termed cerebral ALD, and axonal myeloneuropathy. There is no known association between genotype and phenotype, and therefore while multiple persons may have the same *ABCD*1 pathogenic variant, there is no identified means of determining which males with ALD will develop which clinical features of the disorder. By adulthood, approximately 40% of the patients develop cerebral ALD, a severe, neuroinflammatory condition that is generally progressive and fatal without intervention (Gupta et al., 2022). As elevations in VLCFA were recognized to be present at birth, the potential to use newborn screening for ALD was appreciated (Moser et al., 2016). More than

half of the states in the United States currently screen for ALD and many more have started efforts to incorporate ALD into their current newborn screening protocol (ALD Alliance, 2022).

Cerebral ALD is an inflammatory, demyelinating, progressive leukodystrophy with a mean age of clinical onset of 7.1 years. It is observed in approximately 40% of males with ALD through age 20, although it is also observed in adults with ALD as well. Although the rate of deterioration can be variable, rapid progression is common, with total disability developing by 6 months to 2 years and death within 5 to 10 years of diagnosis (Zhu et al., 2020). Early signs of developing cerebral disease may include impaired ability to sustain attention and focus, declining performance in school, or behavioral concerns such as hyperactivity, irritability, or aggression. The development of neurocognitive and behavioral symptoms is associated with both the extent and the location of the demyelinating lesion. The diagnosis of cerebral ALD is established by MRI. As a demyelinating disease, progressive T1/T2 changes are observed in the white matter. The presence of contrast enhancement is often observed and is thought to be an indication of blood-brain barrier disruption due to active neuroinflammation. Untreated, 85-90% of boys with symptomatic cerebral disease die or progress to a vegetative state within several years (Gupta, 2022). An MRI-based severity score (Loes score) uses a 0-34 point system related to the location and extent of involvement and the presence of atrophy to evaluate the extent of involvement and define progression. The Loes score correlates with clinical findings, as patients with symptomatic disease are likely to have a score of 10 or higher (Moser & Fatemi, 2018). Clinical outcomes have commonly been scored using the ALD-specific neurologic function scale (NFS), that assesses the severity of neurologic dysfunction by assigning scores to 15 different disabilities. Lower scores indicate fewer symptoms, and higher scores indicate a more significant disability. The NFS score can be used to guide the recommendation for hematopoietic stem cell transplantation (HSCT), but there is no score that absolutely determines the decision for HSCT (Zhu et al., 2020).

Allogeneic HSCT can arrest the progression of the neurologic disease when performed in the early stages of cerebral ALD, however the precise mechanism by which that occurs is not clear. The survival advantage of transplantation compared to no transplant in patients with early-stage cerebral ALD was demonstrated in a retrospective analysis by Mahmood et al. in 2007. The projected 5-year survival in the transplanted population was 95% in comparison to 54% in the non-transplanted group. While there are no universally accepted standard criteria for HSCT in boys with cerebral ALD, the general criteria are a genetically and/or clinically confirmed diagnosis of ALD and the presence of cerebral disease that is not advanced, based on neurological symptoms and evidence of cerebral disease on brain MRI with the presence of gadolinium contrast enhancement around a consistent lesion. HSCT is not effective in patients with advanced cerebral ALD. There are drawbacks to allogeneic HSCT. In addition to the lack of efficacy in advanced disease, transplantation does not reverse neurologic findings present at the time of transplant and does not stabilize cerebral disease for 3 to 24 months after stem cell infusion. Symptoms can progress during this time. Treatment failure is usually due to transplant-related complications or rapid disease progression during the engraftment of donor cells (Eichler et al., 2017). Transplant is ineffective for the adrenal manifestations of disease and is not felt to impact the development of adult onset adrenomyeloneuropathy (Zhu et al., 2020).

Treatment

Gene therapy with autologous CD34+ hematopoietic stem cells transduced with a lentiviral vector that contained ABCD1 complementary DNA (cDNA) has shown promising outcomes with patients demonstrating functional expression of ALD protein and disease stabilization. The FDA granted accelerated approval of Skysona based on 24-month Major Functional Disability (MFD)-free survival. Skysona does not prevent the development of or treat adrenal insufficiency due to adrenoleukodystrophy. Skysona carries a black box warning for hematologic malignancy. Several patients have been diagnosed between 14 months and 7.5 years after Skysona administration with hematologic malignancy, including several life-threatening cases of myelodysplastic syndrome. The cancers appear to be the result of the lentiviral vector, Lenti-D, integration in proto-oncogenes. The warning contains specific recommendations for life-long monitoring for malignancy (FDA, 2022).

The safety and efficacy of Skysona was assessed in two 24-month, open-label, single-arm studies in patients with early, active CALD as defined by Loes score between 0.5 and 9 and gadolinium enhancement (GdE+) on MRI, and a NFS of ≤ 1. The patients enrolled and treated with Skysona (study 1, n = 32; study 2, n = 35) all had elevated VLCFA

levels and confirmed mutations in the *ABCD*1 gene. Grade 3 or higher infections occurred in 21% of patients (12% bacterial, 3% viral, and 6% unspecified). The most common Grade 3 or higher infections were vascular device infections (7% of patients) diagnosed as late as 6 months after treatment and bacteremias (6% of patients) diagnosed as late as 8 months after treatment. Febrile neutropenia developed within 2 weeks after Skysona infusion in 72% of patients. Grade 3 or higher cytopenias on or after 60 days following treatment occurred in 47% of patients and included low platelet count (14%), low neutrophil count (22%), low lymphocyte count (27%), and low hemoglobin (2%). Grade 3 cytopenias persisted beyond Day 100 in 15% of patients and included low platelet count (7%), low neutrophil count (9%), and low lymphocyte count (6%). Serious adverse reactions of pancytopenia occurred in two patients who required support with blood and platelet transfusions as well as growth factors (FDA, 2022).

A post-hoc enrichment analysis in symptomatic patients compared time from onset of symptoms (NFS ≥ 1) to time to first MFD or death in Skysona treated and natural history patients. The MFDs are defined as: loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement. To be included in the analysis, patients had to have symptoms at baseline (NFS = 1) or be asymptomatic (NFS = 0) at baseline and have developed symptoms (NFS ≥ 1) during the course of follow-up in the study. Additionally, they had to have at least 24 months of follow-up after NFS ≥ 1 or have had an event (MFD or death). Slower progression to MFD or death from time of symptom onset (first NFS ≥ 1) was seen for early, active CALD patients treated with Skysona compared to a similar natural history of disease. There were insufficient data beyond 24 months for the symptomatic Skysona subpopulation to assess long-term MFD-free survival as compared to the natural history of disease. There was insufficient duration of follow up to assess efficacy in Skysona treated patients who remained asymptomatic. There were insufficient data to compare relative efficacy of Skysona to allogeneic HSCT (FDA, 2022).

An increase in cancer cases among Skysona-treated patients with early, active CALD prompted an FDA investigation and subsequent safety communication in November 2024. At the time of initial approval of Skysona in 2022, hematologic malignancy was identified as a serious risk, with MDS reported in 3 of 67 patients (4%) across clinical studies. Since initial approval, FDA received 7 additional reports from clinical trial participants, and as of July 2025, hematologic malignancies have been diagnosed in 10/67 (15%) clinical trial participants. Current reports suggest the time to diagnosis of hematologic malignancy ranges from 14 months to 10 years following Skysona administration. Nine of the ten patients have been treated with allo-HSCT (with or without chemotherapy) for the malignancy. The malignancies are life-threatening conditions, and one death related to treatment for malignancy has occurred to date. In some cases, patients developed malignancy before Skysona had time to potentially provide therapeutic benefit for their CALD (FDA, 2025). Duncan et al. (2024) recently reviewed the clinicopathological and genetic features of seven cases of hematologic cancer (as of April 25, 2024) in patients who received Skysona (one patient in the ALD-102 study and six patients in the ALD-104 study). Most patients who received treatment in the ALD-102 and ALD-104 studies benefitted clinically, with 81% 4-year survival free of major functional disabilities and hematologic cancer, and without referral for allo-HSCT. In the subgroup of patients in whom hematologic cancer developed, the cases were associated with clonal vector insertions within oncogenes and clonal evolution with acquisition of somatic genetic defects.

Elivaldogene autotemcel (SKYSONA®) is considered medically necessary as a one-time single dose to slow the progression of neurologic dysfunction in patients with early, active cerebral adrenoleukodystrophy meeting all of the following:

- Patient is without an available human leukocyte antigen (HLA)-matched donor for allogeneic hematopoietic stem cell transplant.
- Male aged 4 – 17 years.
- Asymptomatic or mildly symptomatic with neurologic function score ≤ 1.
- Loes scores of 0.5 – 9.
- Gadolinium enhancement on brain MRI.
- Presence of a pathogenic (or likely pathogenic) variant in the *ABCD* 1 gene as detected by genetic testing.
- Elevated very long chain fatty acid (VLCFA) levels.

- Documentation that an evaluation for adequate hematological function has been completed and clearance obtained.
- Documentation that abnormal liver function has been evaluated by hepatology and clearance obtained.
- Patients with a known prior or current malignancy must undergo an oncology evaluation. Oncology clearance must include an assessment indicating the malignancy will not have any anticipated effect on survival.

Because of the risk of hematologic malignancy, consultation with hematology experts is highly recommended prior to Skysona treatment to inform benefit-risk treatment decision and to ensure adequate post-treatment monitoring.

Metachromatic leukodystrophy

Metachromatic leukodystrophy (MLD) is an autosomal recessive hereditary neurodegenerative disease caused by mutations in the arylsulfatase-A *(ARSA*) gene affecting the production of the enzyme ARSA; it is sometimes caused by mutations in *PSAP* genes. MLD belongs to the group of lysosomal storage diseases (LSDs). With a prevalence rate of 1 in 40,000 – 160,000 worldwide, MLD is one of the most common leukodystrophies (Institute for Clinical and Economic Review [ICER], 2023). The disease is characterized by the damage of the myelin sheath that covers most of the nerve fibers of the central (CNS and peripheral (PNS) nervous systems, leading to progressive motor and cognitive impairments as clinical manifestations (Shagimuratova et al., 2020). The clinical subtypes of MLD are characterized by age at onset. The most common and aggressive subtype is late infantile (LI-MLD) (50-60% of patients) in which symptoms start before 30 months and children lose the ability to walk and swallow within 1-2 years. Juvenile MLD is divided into two subsets: early juvenile (30 months to 6 years) and late juvenile (7 – 16 years). In the early juvenile subtype (EJ-MLD), significant disability occurs within 3 years of symptom onset. Early symptoms of both subtypes include low motor tone, losing or failing to achieve motor and cognitive milestones, and behavioral and cognitive problems that may manifest as difficulties in school. Those exhibiting symptom onset ≥ 17 years of age are considered to have adult MLD (Fumagalli, 2022). As the disease progresses, difficulty swallowing and breathing may eventually lead to gastrostomy tubes, suctioning, and ventilatory support (MLD Foundation, 2024). Mean survival varies based on subtype, with LI-MLD children surviving around 8 years and those with EJ-MLD 10-20 years (ICER, 2023). According to the MLD Foundation (2024), LI-MLD is often not properly diagnosed prior to death of the patient and later onsets of MLD are often misdiagnosed as ADHA, ADD, or psychiatric conditions. This suggests the frequency of both subtypes might be underreported. Currently no states require newborn screening for MLD.

Treatment

Atidarsagene autotemcel (Lenmeldy™) is a gene therapy containing autologous hematopoietic stem and progenitor cells (HSPCs) that have been transduced with a lentivirus vector containing the human *ARSA* gene. The HSPCs are isolated from bone marrow or mobilized peripheral blood enriched for CD34+ cells through apheresis. A minimum of 1-10 x 10^6 cells/kg are needed to manufacture the gene therapy. The resulting genetically modified HSPCs are able to synthesize functional enzymes. Prior to infusion of Lenmeldy, patients undergo myeloablative conditioning to remove the native HSPCs that carry the defective *ARSA* gene. Treatment consists of a single intravenous infusion of Lenmeldy. The genetically modified HSPCs are able to repopulate the hematopoietic space. Certain populations of genetically modified blood cells are able to cross the blood-brain barrier to engraft in the central nervous system. It is anticipated that successful and stable engraftment of the genetically modified cells should produce a persistent therapeutic effect (Hayes, 2024; FDA, 2024).

The safety and efficacy of Lenmeldy was assessed in 39 children across two single-arm, open-label clinical trials and a European Union (EU) expanded access program (EAP). Two children with advanced disease were excluded from the efficacy analysis. The clinical trials enrolled 13 children with pre-symptomatic late infantile (PSLI), 6 children with pre-symptomatic early juvenile (PSEJ) and 9 children with early symptomatic early juvenile (ESEJ) MLD. The EU EAP enrolled 7 children with PSLI, 1 child with PSEJ and 1 child with ESEJ MLD. All children had documented biochemical and molecular diagnosis of MLD based on ARSA activity below the normal range and identification of two disease-causing *ARSA* alleles. The major efficacy outcomes were motor and neurocognitive function as assessed by Gross Motor Function Classification in Metachromatic Leukodystrophy (GMFA-MLD) levels and standard scores on age-appropriate neurocognitive tests, respectively. The efficacy of Lenmeldy was compared to an external untreated natural history (NHx) cohort of children with LI (n=28) and EJ (n=21) MLD. Data from the NHx cohort were collected

both retrospectively and prospectively. Cognitive outcomes in the children with PSEJ and ESEJ MLD were compared to outcomes for untreated children reported in the medical literature (Fumagalli et al., 2022; FDA 2024).

In the PSLI cohort the primary endpoint was severe motor impairment-free survival, defined as the interval from birth to the first occurrence of loss of locomotion and loss of sitting without support (GMFC-MLD level ≥ 5) or death. Treatment with Lenmeldy significantly extended severe motor impairment-free survival in this cohort compared with untreated LI natural history children. Seventeen children with PSLI MLD treated with Lenmeldy have been followed until at least age 5 years. At the age of 5 years, 100% of Lenmeldy treated PSLI children remained event-free compared with 0% of untreated LI children. Additionally, 12 out of 17 children who were at least 5 years of age at last follow-up (ages 5.4-13.3 years of age) retained independent ambulation (GMFC-MLD level ≤1). Two children at the time of last assessment (ages 8.1 and 11.6 years) were able to ambulate with support (GMFC-MLD level 2). Loss of ambulation without support occurred at 3.6 and 7.8 years of age, respectively. One child had progressed to GMFC-MLD level 5 by age 7.2 years and lost all motor function at age 9.9 years. Two children never achieved independent ambulation. In terms of cognitive function, performance was captured by neuropsychological tests according to age and/or ability. Cognitive function was defined using the following: normal cognitive function, standard score ≥ 85; mild impairment, standard score ≥ 70 and < 85; moderate impairment, score > 55 and < 70; severe cognitive impairment, score ≤ 55. Nineteen of 20 children with PSLI MLD had performance standard scores above the threshold of sever impairment through to the last follow-up. At last assessment, two of these children were below the threshold for moderate cognitive impairment, with all others maintaining performance standard scores ≥ 70 and most maintaining normal scores (≥ 85). These outcomes contrast significantly with results in LI NHx children with completed neuropsychological assessments who demonstrate severe cognitive impairment early in their disease process (FDA, 2024).

Seven children with PSEJ MLD were treated with Lenmeldy. One child died at age 2.1 years from a cerebral infarction. There were insufficient data in three children who were too young at last follow-up to evaluate efficacy as symptom onset may not begin until seven years of age in EJ MLD. One child had evaluable motor outcomes, but while showing stable normal cognitive function, was neither old enough nor had sibling data for cognitive events to be evaluable. Three children had evaluable outcomes: one treated at age 4.1 years retained normal gait at 11.9 years; one treated at 3.6 years retained normal gait at 7.3 years; and one treated at 5.6 years retained normal gait at 13.6 years. Two children had evaluable cognitive function: one treated at 4.1 years retained stable normal cognitive function at 11.9 years and one treated at 5.6 years retained stable normal performance standard score at 11.4 years (FDA, 2024).

In the ESEJ MLD population, four of ten children had favorable cognitive outcomes after treatment in the setting of motor decline. Retention of cognitive functioning has not been reported in this phase of EJ MLD disease, as motor and cognitive function typically decline together in untreated children (FDA, 2024). An ICER analysis (2024).

Atidarsagene autotemcel (Lenmeldy™) is considered medically necessary as a one-time infusion for the treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy when the following criteria are met:

- Diagnosis of pre-symptomatic disease (PSLI or PSEJ) is confirmed through one of the following:
  - Testing of siblings of a previously affected and diagnosed child **OR**
  - Positive newborn screening and, if positive, formal diagnostic confirmation testing
- Patients diagnosed with early symptomatic early juvenile (ESEJ) meet all of the following:
  - GFMA-MLD 0-1 **AND**
  - IQ ≥ 85

Note: Exceptions for impairments due to non-MLD comorbidities (e.g., motor impairments that are due to comorbid neuromuscular disease) or patients close to the IQ cutoff will be considered.

Atidarsagene autotemcel (Lenmeldy™) is considered unproven due to a lack of sufficient evidence in the following:

- Children with late juvenile MLD
- Patients with adult MLD

- Children or adults who received treatment within the last six months and with residual cells of donor origin

Recessive dystrophic epidermolysis bullosa (RDEB)

Epidermolysis bullosa (EB) is a genetic skin disorder characterized by extremely fragile skin leading to blisters, erosions, chronic ulcerations, and scars from mechanical trauma or friction. There are four main types of EB: EB simplex (EBS), dystrophic EB (DEB), junctional EB (JEB), and Kindler syndrome. EB symptoms most often begin at birth or during infancy and can vary significantly in severity depending on type and subtype. In some cases, EB is fatal. An estimated 200 children per year are born with EB. (National Organization for Rare Disorders [NORD], 2024; Dystrophic Epidermolysis Bullosa Research Association of America [DEBRA], 2021). Recessive DEB (RDEB) is the focus of this clinical guideline.

Recessive dystrophic epidermolysis bullosa is the result of mutations in the *COL7A1* gene that severely reduce or prevent the production of type VII collagen (C7) which forms anchoring fibrils that are essential to dermal-epidermal adhesion. The diagnosis of RDEB is established with characteristic clinical findings and biallelic *COL7A1* pathogenic variants (Lucky et al., 2025). In addition to scarring, milia, mucous membrane involvement and nail dystrophy, common manifestations include malnutrition, anemia, esophageal strictures, growth retardation, webbing or fusion of fingers and toes causing mitten deformity (pseudosyndactyly) with loss of function, development of contractures, malformation of teeth, microstomia and corneal abrasions. These manifestations arise from deficiency in anchoring function by the loss of C7 in the tissues. However, other organs with minimal or residual C7 expression, such as the heart in dilated cardiomyopathy, kidneys in IgA nephropathy, and the auditory system in hearing loss, can also be affected in DEB. Additionally, the biochemical, organizational, and mechanical properties of the extracellular matrix at the site of chronic wounds support the development of cutaneous squamous cell carcinomas [cSCC] (Guerra et al., 2017; Nyström, 2024) and subsequently their transition into metastatic high-risk tumors, which are the leading cause of death for those with severe RDEB (Harrs et al., 2022).

Treatment

Standard of care is supportive and includes wound care, protective bandaging, infection control, pain management, maintaining proper nutrition, physical and/or occupational therapy, and monitoring for SCC development. Whenever possible, supportive care should be provided or managed by a specialized EB treatment center (NORD, 2024). In 2023, the FDA approved beremagene geperpavec (Vyjuvek®), a herpes-simplex virus type 1 (HSV-1) vector-based topical therapy that delivers new *COLA7A1* genes directly to DEB skin wounds to promote healing in patients 6 months of age and older. Vyjuvek is applied weekly to a maximum dose based on age and wound size. At this time, the indications and use of Vyjuvek are out of scope for this guideline.

Prademagene zamikeracel (Zevaskyn™) is a cutaneous gene therapy constructed of autologous skin sheets transduced with a retroviral vector (LZRSE) carrying normal copies of the *COLA7A1* gene. The sheets are designed to be grafted onto RDEB wounds with the therapeutic goal of restoring functional C7 expression and subsequent C7 assembly into anchoring fibrils that secure the epidermal basement membrane to the dermis (Abeona Therapeutics Inc., 2025). Zevaskyn is manufactured using two small (8 mm) skin biopsies obtained from intact, unscarred sites. Biopsy samples are shipped to the manufacturer where keratinocytes are isolated, harvested, cultured, and transduced with a *COLA7A1*-containing retrovirus. The cells are cultured into 5 x 7 cm gene-modified epidermal sheets expressing normal C7. Up to 12 sheets are manufactured from the biopsies. The manufacturing process takes approximately 25 days. Cultured sheets are surgically grafted onto the RDEB wounds under general anesthesia within 36 hours of completion of the manufacturing process. It is not currently anticipated that storage beyond 36 hours will be possible as no studies have been done to assess long-term viability of the cultured sheets.

Some patients may require ~2 treatment cycles to cover their existing wounds and additional treatment is needed for new wounds arising from previously untreated surfaces. Patients remain hospitalized for at least one week postoperatively to optimize engraftment (Abeona Therapeutics, 2024).

The best available published evidence evaluating Zevaskyn (referred to as EB-101 in study publications) for the treatment of RDEB is limited to one phase I/IIa single-center nonrandomized open-label study enrolling 7 adults with severe generalized RDEB. Eligible patients had RDEB wounds with a total area of at least 100 cm^2 that were present and unhealed for at least 12 weeks. Expression of the noncollagenous domain 1 of type VII collagen (C7) was

required for study inclusion. Patients with antibodies to C7 as well as those with evidence or a history of SCC in wounds designated for treatment were excluded. Seven patients and 42 target wounds were treated in the study; 4 patients were enrolled and treated during phase 1 and 3 more after the study advanced to phase IIa. In the phase I segment, EB-101- cultured sheets were grafted onto 5 chronic open wound sites and 1 induced wound site for a total of 24 treated wounds. In the phase IIa segment, EB-101- cultured sheets were grafted onto 6 chronic open wound sites for a total of 18 treated wounds. In total, 38 chronic wounds and 4 induced wounds were treated. The primary endpoint was Investigator Global Assessment (IGA) of wound healing at graft sites compared to baseline. Compared with baseline, wound healing of at least 50% was attained in 92.9% of the 42 wounds treated with EB-101 within 6 months of grafting. By follow-up year 5, wound healing rates had slightly declined; 70% of 30 assessable wounds had at least 50% healing and 63.3% had at least 75% healing, compared with baseline. Surface area wound healing outcomes, assessed with Canfield Vectra photography software, are not reported in full; selected photographs of treated sites on 3 patients have been published. At 5-year follow-up, improved patient-reported outcomes for pain and itch were significantly associated with improved wound healing. No serious adverse events related to treatment were reported. Two patients developed SCC at locations distant to the graft sites and were deemed unrelated to treatment. During follow up, two patients died: one from sepsis and the other from malnutrition. Both deaths were determined to be unrelated to treatment (Siprashvili et al., 2016; Eichstadt et al., 2019; So et al., 2022).

Results from the pivotal VIITAL study are not published to date but were presented at the International Societies for Investigative Dermatology meeting in May 2023. Tang and colleagues (2023) reported outcomes in 43 randomized wounds in 11 patients treated with EB-101-cultured sheets and 43 paired control wounds receiving standard of care. At week 24 with confirmation ≥2 weeks later 81.4% (35/43) of EB-101-treated wounds had ≥50% healing from baseline vs 16.3% (7/43) of control wounds (P<0.0001; coprimary endpoint); wound healing ≥75% from baseline was achieved in 65.1% of EB-101-treated wounds vs. 7.0% of controls (P<0.0001); and complete wound healing was achieved in 16.3% of EB-101-treated wounds vs. 0% of controls (P=0.0160). Mean pain, assessed on a 0-10 scale, was reduced from baseline to week 24 by 3.07 for EB-101-treated wounds (n=43) vs. 0.90 for controls (n=42), with a mean pairwise difference of 2.23 (P=0.0002; coprimary endpoint). Published peer-reviewed results of the VIITAL study outcomes are needed to confirm these results.

Prademagene zamikeracel (Zevaskyn™) is considered medical necessary as a surgical application of up to 12 gene-corrected keratinocyte sheets applied during a single surgical session in pediatric and adult patients with recessive dystrophic epidermolysis bullosa wounds when the following criteria are met:

- Confirmed positive expression of the non-collagenous region 1 of the type 7 collagen protein (NC1+) in the skin.
- Two confirmed RDEB C7 mutations with recessive inheritance patterns **OR** confirmation that parents don't have any evidence of dominant disease.
- No current evidence of systemic infection including human immunodeficiency virus (HIV), hepatitis B or hepatitis C.
- No current evidence or a history of squamous cell carcinoma (SCC) in the targeted treatment areas.
- The targeted treatment areas have not been previously treated with Zevaskyn.

Additional prior authorization is required for the following:

- A second treatment cycle to cover existing wounds.
- Treatment of new wounds arising from previously untreated sites.

Sickle cell disease

Sickle cell disease is a Mendelian genetic disorder. A mutation in the b-hemoglobin gene is responsible for the synthesis of sickle hemoglobin (HbS). In all sickle cell genotypes, at least 50% of the patient's hemoglobin is HbS. Deoxygenated HbS forms polymers that deform erythrocytes. Most of the damaged erythrocytes are trapped and hemolyzed in the reticuloendothelial system, but 30% of the hemolysis is intravascular. This leads to microvascular occlusion, abnormal regulation of erythrocyte volume, reduced bioavailability of nitric oxide, ischemia-reperfusion injury, inflammation and oxidant damage, abnormal intercellular interactions, endothelial injury, and leukocyte and platelet activation. The most common genotype in sickle cell disease is HbSS, in which HbS constitutes the majority of

the hemoglobin produced. One third of affected persons inherit compound heterozygous forms of sickle cell disease characterized by a combination of HbS and HbC (HbSC), a combination of HbS and b+ thalassemia (HbSb+), or less commonly, combinations of HbS and other hemoglobin variants. The HbS gene is common in the Caribbean, Central and South America, the Middle East, Africa, and India. In African Americans, the prevalence of HbSS is approximately 1 in 600, and the prevalence of all disease genotypes approaches 1 in 300. In the United States, the near-universal survival of children with sickle cell disease into adulthood is creating a growing population of adults with the disease. (Pecker & Lanzkron, 2021).

Treatment of acute and chronic complications of sickle cell disease include: Oxbryta® (voxelotor) in adults and children 12 years and older; Adakveo® (crizanlizumab-tmca) to reduce the frequency of vaso-occlusive crises in adults and pediatric patients, aged 16 years and older in adults and children 16 years and older; and SKILOS® (hydroxyurea) to reduce the frequency of painful crises and reduce the need for blood transfusions in children, 2 years of age and older, and Endari™ (L-glutamine oral powder) to reduce the acute complications of sickle cell disease in adult and pediatric patients five years of age and older (Pecker & Lanzkron, 2021). In addition, transfusion therapy has been used to treat acute and chronic complications, however significant questions persist about how best to use red cell transfusions to prevent pain, pregnancy complications, acute chest syndrome, and priapism (Chou & Fasano, 2016). Allogeneic hematopoietic stem cell (HSC) transplantation can cure SCD, but less than 20% of eligible patients have a related HLA-matched donor (Frangoul et al., 2021).

Patients with SCD contend with multiple acute and chronic systemic complications including severe pain and damage to critical organs including the heart and kidneys. The most common complication of SCD is an acute episode of severe pain referred to as an acute vaso-occlusive crisis (VOC). A VOC is defined as pain resulting from tissue ischemia caused by vaso-occlusion most commonly in the bone(s) and bone marrow (NIH, 2014). Acute pain episodes occur in > 90% of patients with SCD. Other complications include delayed growth and puberty, spleen damage leading to infections including chlamydia, *Hemophilus influenzae* type B, salmonella, and staphylococcus, avascular or aseptic necrosis leading to joint damage, hypertension which increases the risk of stroke and heart attack, acute chest syndrome (sometimes fatal), retinopathy, intrahepatic cholestasis, pregnancy problems including risk of miscarriage, premature birth, and low birth weight babies, and serious anemia problems (Pecker & Lanzkron, 2021).

Treatments

Exagamglogene autotemcel (Casgevy™) has been previously described.

Safety and efficacy of a single infusion of Casgevy was evaluated in an ongoing single-arm, multi-center trial enrolling adults and adolescent patients with SCD. Patients were followed for 24 months after infusion and were subsequently encouraged to enroll in a second trial (NCT00208529), an on-going long-term follow-up for an additional 15 years.

Eligible patients had a history of at least two protocol-defined severe VOC events during each of the two years prior to screening. Severe VOC in this trial was defined as an occurrence of at least one of the following:

- Acute pain event requiring a visit to a medical facility and administration of opioid or IV NSAIDs or RBC transfusions
- Acute chest syndrome
- Priapism lasting > 2 hours and requiring a visit to a medical facility
- Splenic sequestration

At the time of interim analysis, based on June 2023 data cut-off date, a total of 63 patients enrolled in the trail, of which 58 (92%) patients started mobilization. A total of 44 (76%) patients received Casgevy infusion and formed the full analysis set (FAS). Thirty-one patients from the FAS (70%) had adequate follow up to allow evaluation of the primary endpoint and formed the primary efficacy set (PES), defined as all patients who had been followed for at least 16 months after infusion. The PES also included patients who had less than 16 months follow-up due to death of discontinuation due to Casgevy-related adverse events or continuously received RBC transfusions for more than 10 months after infusion.

An interim analysis was conducted with 31 patients from the PES. The median total duration of follow-up was 19.3 (0.8, 48.1) months from the time of infusion in FAS. There were no cases of graft failure or graft rejection. The primary efficacy outcome was the proportion of patients who did not experience any protocol-defined severe VOCs for at least 12 months within the first 24 months after infusion (VF12 responders). The proportion of patients who did not require hospitalization due to severe VOCs for at least 12 consecutive months within the 24-month evaluation period (HF12) was also assessed. Evaluation of VF12 and HF12 began 60 days following the last RBC transfusion for post-transplant support or SCD management. The median time to the last RBC transfusion was 19 (11, 52) days following Casgevy infusion for the PES.

The VF12 response rate was 29/31 (93.5%, 98% one-sided CI: 77.9%, 100.0%). The 29 VF12 responders did not experience protocol-defined severe VOCs during the evaluation period with a median duration of 22.2 months at the time of interim analysis. One VF12 responder, after initially achieving a VF 12 response, experienced an acute pain episode meeting the definition of a severe VC at month 22.8 requiring a 5-day hospitalization. Of the 31 patients evaluable for VF12 response, one patient was not evaluable for HF12 response: the remaining 30 patients (100% [98% one-sided CI: 87.8%, 100%]) achieved the endpoint of HF 12. No Casgevy-related serious adverse events. One patient died due to a COVID-19 infections followed by respiratory failure which was determined unrelated to Casgevy (FDA, 2023).

Exagamglogene autotemcel (Casgevy™) is considered medical necessary as a one-time infusion in patients 12 years of age and older with a diagnosis of SCD who meet the following:

- One of the following genotypes confirmed by molecular or genetic testing
  - βs/βs
  - βs/β0
  - βs/β+
- Documentation of a minimum of two severe VOC events during each of the previous two years. A VOC is defined as an occurrence of at least one of the following events:
  - Acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or IV NSAIDs) OR RBC transfusions
  - Acute chest syndrome
  - Priapism lasting > 2 hours and requiring a visit to a medical facility
  - Splenic sequestration
- Documentation of confirmative screening showing the patient does not have any of the following infectious diseases:
  - HIV-1
  - HIV-2
  - HBV
  - HCV
- Treatment plan includes documentation of intent to transfuse patient prior to apheresis with a goal to maintain HbS levels < 30% of total Hb while keeping total Hb concentration ≤ 11 g/dL.
- Documentation that the patient is a candidate for an allogeneic HSCT, but ineligible due to absence of an appropriate donor
- Documentation of compliance with hydroxyurea or another prescribed treatment regimen
- Patient has not previously received gene therapy for the requested diagnosis

Lovotibeglogene autotemcel (Lyfgenia™) is a $\beta^{A\text{-}T87Q}$-globin gene therapy prepared using the patient's own HSCs which are enriched for CD34+ cells, then transduced *ex vivo* with BB305 LVV. The promotor, a regulatory element that controls the expressions of the transgene selected for BB305 LVV, is a cellular (non-viral) promotor that controls gene expression specific to the erythroid lineage cells. BB305 LVV encodes $\beta^{A\text{-}T87Q}$-globin.

Lyfgenia adds functional copies of a modified β^{A}-globin gene into patients HSC through transduction of autologous CD34+ cells with BB305 LVV. Following infusion, the transduced CD34+ HSCs engraft in the bone marrow and differentiate to produce red blood cells containing biologically active $\beta^{A\text{-}T87Q}$-globin that will combine with α-globin to

produce functional Hb containing $\beta^{A\text{-}T87Q}$-globin (HbA^{T87Q}). HbA^{T87Q} has similar oxygen-binding affinity and oxygen hemoglobin dissociation curve to wild type HbA, reduces intracellular and HbS levels, and is designed to sterically inhibit polymerization of HbS thereby limiting the sickling of red blood cells. Lyfgenia has not been studied in patients with more than two α-globin gene deletions.

The efficacy of Lyfgenia was studied in a single-arm, 24-month, open-label, multicenter Phase 1/2 study (Study 1-C) and continued on a long-term follow-up study. In Study 1-C, 43 subjects underwent apheresis after mobilization of which 36 patients received myeloablative busulfan conditioning. Seven patients did not proceed to conditioning: 2 patients discontinued due to apheresis-related issues and 5 discontinued at patient and/or physician discretion. Thirty-six patients received intravenous infusion of Lyfgenia.

The transplant population for vaso-occlusive events (VOE) efficacy outcomes included patients with a history of at least 4 VOEs in the 24 months prior to informed consent. Efficacy outcomes were complete resolution of VOEs (VOE-CR) and severe VOEs (sVOE-CR) between 6 months and 18 months following infusion. VOEs were defined as any of the following events requiring evaluation at a medical facility:

- 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

Severe VOE (sVOE) were defined as either of the following events:

- VOE requiring a hospitalization or multiple visits to an emergency department/urgent care over 72 hours and receiving IV medications at each visit
- Priapism requiring any level of medical attention

Globin response (GR) was defined as meeting the following criteria for a continuous period of at least 6 months after infusion:

- Weighted average hemoglobin A^{T87Q} percentage of non-transfused total Hb ≥ 30% **AND**
- Weighted average non-transfused total Hb ($HbS+HBF+HbA_2+HbA^{T87Q}$) increase of ≥ 3 g/dL compared to baseline total HB **OR** weighted average non-transfused total Hb ≥ 10 g/dL

All 36 patients infused in Study 1-C were evaluated for globin response. 31/36 (86%) achieved GR. All patients maintained GR once it was achieved.

Three patients died during Lyfgenia clinical trials; one from sudden cardiac death due to underlying disease and two from acute myeloid leukemia (AML) who were treated with an earlier version of Lyfgenia. Two patients developed anemia following treatment; one patient requires monthly pRBC transfusions. The other was diagnosed with myelodysplastic syndrome (MDS). Both patients had α-thalassemia trait.

The median (min, max) duration of follow-up for the 36 patients in Study 1-C is 38 (12, 61) months post infusion. Following the primary evaluation period to last follow-up, 4 of 32 patients who achieved VOE-CR experienced VOEs while maintaining GR. After the primary evaluation period up to 24 months, 17 of 35 (49%) patients were prescribed opioids for sickle cell and non-sickle cell-related pain (FDA, 2023).

Lovotibeglogene autotemcel (Lyfgenia™) is considered medically necessary as a one-time infusion in patients 12 years of age and older with a diagnosis of SCD who meet the following:

- One of the following genotypes confirmed by molecular or genetic testing
    - βs/βs
    - βs/β0
    - βs/β+

- Documentation of a minimum of 4 VOEs within the prior 24 months. A VOE is defined as at least one of the following:
    - An episode of acute pain with no medically determined cause other than vaso-occlusion, lasting more than two 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 IV medications at each visit
    - Priapism requiring any level of medical attention
- Documentation of confirmative screening showing the patient does not have any of the following infectious diseases:
    - HIV-1
    - HIV-2
    - HBV
    - HCV
- Treatment plan includes documentation of intent to transfuse patient to a target of 8-10 g/dL, not to exceed 12 g/dL, and HbS of < 30% to reduce the risk of SCD-related complications.
- Documentation that the patient is a candidate for an allogeneic HSCT, but ineligible due to absence of an appropriate donor.
- Documentation of compliance with hydroxyurea or another prescribed treatment regimen.
- Patient has not previously received gene therapy for the requested diagnosis.

NOTE: Lyfgenia carries a boxed warning. Hematologic malignancy has occurred in patients treated with Lyfgenia (Study 1, Group A). Two patients treated with an earlier version of Lyfgenia using a different manufacturing process and transplant procedure developed AML. One patient with α-thalassemia trait has been diagnosed with myelodysplastic syndrome (MDS). Patients must be monitored closely for evidence of malignancy through complete blood counts every 6 months for at least 15 years after treatment with Lyfgenia, and integration site analysis at months 6, 12, and as warranted.

Wiskott-Aldrich Syndrome

Wiskott–Aldrich syndrome (WAS) is a rare, X linked primary immunodeficiency caused by pathogenic variants in the WAS gene, which encodes the Wiskott–Aldrich syndrome protein (WASp). Diagnosis is based on a combination of clinical findings, laboratory evaluation, and genetic testing. Key laboratory features include persistent thrombocytopenia with abnormally small platelets, immune globulin abnormalities (often elevated IgE, low IgM), and impaired cellular and humoral immune responses. Definitive diagnosis requires identification of a pathogenic WAS variant by molecular genetic testing, with assessment of WASp expression by flow cytometry used as supportive evidence. (Buchbinder, et al., 2022)

The disease classically presents with the triad of microthrombocytopenia, eczema, and immunodeficiency; however, the clinical phenotype spans a broad spectrum ranging from severe, life-threatening disease expression to milder forms. The condition occurs almost exclusively in males due to its X-linked recessive inheritance, with an estimated incidence of approximately 1 in 100,000 live male births in the United States and Europe. Although WAS affects individuals of all ethnic backgrounds, milder presentations may be underrecognized or misdiagnosed as immune thrombocytopenia (ITP) in early childhood. Improvements in supportive care, infection prophylaxis, hematopoietic stem cell transplantation (HSCT), and emerging gene therapy approaches have contributed to increased overall survival in recent years (Buchbinder et al., 2022).

Symptoms typically manifest in infancy or early childhood. Bleeding complications—such as petechiae, epistaxis, bloody diarrhea, gastrointestinal hemorrhage, and, in severe cases, intracranial hemorrhage—occur due to thrombocytopenia and platelet dysfunction. Eczema is often severe and difficult to control with standard dermatologic therapies. Immunodeficiency predisposes patients to frequent and sometimes severe bacterial, viral, and fungal infections including otitis media, pneumonia, sepsis, herpesvirus infections, and Pneumocystis jirovecii pneumonia. Immune dysregulation can lead to autoimmune manifestations such as autoimmune hemolytic anemia, immune thrombocytopenia, vasculitis, and inflammatory bowel disease. Individuals with classic WAS also face a substantially increased lifetime risk of hematologic malignancies, particularly Epstein–Barr virus–associated B-cell lymphomas and leukemias (Dalal et al., 2021). Supportive management includes infection prophylaxis, immunoglobulin replacement therapy, prompt treatment of infections, bleeding precautions, and management of eczema and autoimmune manifestations. Splenectomy may improve platelet counts in select patients but increases infection risk and is used cautiously. Allogeneic HSCT remains the standard curative therapy for patients with severe WAS, particularly when performed early in life using an HLA-matched donor. Outcomes are excellent in younger patients without advanced disease complications. (Dalal, et al., 2021)

Treatment

The efficacy of WASKYRA was evaluated using data from two clinical studies and an expanded access program. Study 1 (NCT01515462) was a prospective, open-label, single-arm, single-center study assessing the safety and efficacy of the fresh formulation compared with each patient's 12-month pretreatment period. Study 2 (NCT03837483) is an ongoing open-label, single-arm, multicenter study that evaluates the cryopreserved formulation using the same 12-month pretreatment comparison. Additional evidence was obtained through an expanded access program. Across all programs, twenty-seven patients were enrolled, and twenty-six received WASKYRA and were included in the efficacy analysis. The median age of treated patients was 2.6 years, with a range from 1 to 35 years. All patients were male, and the study population was racially diverse.

Eligible participants had genetically confirmed Wiskott–Aldrich syndrome and met at least one severity criterion, including a Zhu clinical score of 3 or greater, the presence of a severe WAS mutation, or absent WASP expression, and all lacked a suitable HLA-matched donor. Patients were excluded if they had undergone allogeneic hematopoietic stem-cell transplantation within six months, had residual donor-derived cells, had received prior gene therapy, were HIV positive, or had cytogenetic abnormalities. Hematopoietic stem cells were collected via bone marrow harvest, apheresis after mobilization, or both. Prior to WASKYRA infusion, all patients received a standardized conditioning regimen consisting of rituximab on Day –22, pharmacokinetically guided busulfan from Days –4 to –2 targeting a cumulative

AUC of 48,000 ±10% ng·h/mL per hour, and fludarabine on Days –4 and –3 for a total dose of 60 mg/m². Patients then received a single infusion of WASKYRA at doses ranging from 7 to 31 × 10^6 CD34+ cells/kg, with a median dose of 16.9 × 10^6 cells/kg.

The primary efficacy endpoints assessed clinical outcomes before and after treatment, focusing on the rate of severe infections during the 6–18-month post-treatment period and the rate of moderate or severe bleeding episodes during the 12-month post-treatment period. The rate of severe infections was reduced substantially, declining from 2.0 infections per patient-year of observation in the pretreatment period (95% CI: 1.50, 2.61) to 0.2 infections per patient-year in the 6–18-month period following WASKYRA infusion (95% CI: 0.04, 0.40). A clinically meaningful reduction in bleeding complications was also observed, with moderate or severe bleeding events decreasing from 2.0 events per patient-year before treatment (95% CI: 1.50, 2.61) to 0.8 events per patient-year in the 12 months after gene therapy (95% CI: 0.49, 1.22). These findings demonstrate that WASKYRA results in significant reductions in both severe infections and clinically important bleeding events among patients with Wiskott–Aldrich syndrome who lack suitable matched donors. (FDA, 2025)

Etuvetidigene autotemcel (Waskyra™) is considered medically necessary as a one-time infusion in pediatric patients aged 6 months and older and adults with Wiskott-Aldrich Syndrome when all of the following are met:

- Confirmed mutation on the WAS gene AND at least one of the following:
  - Severe clinical score (Zhu clinical score ≥ 3)
  - Severe WAS mutation
  - Absent WASp expression
- Member is an appropriate candidate for hematopoietic stem cell transplant however no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available
- Member has not received a HSCT within the 6 months prior to planned Waskyra infusion
- There is no evidence of residual cells of donor origin from prior HSCT regardless of time since transplant
- Member has not received prior gene therapy

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Review and Approval History

Version	Date and Description of Activity
1.0	**11/03/2022:** New guideline. Approved by Medical Technology Assessment Committee
1.0	**12/19/2022:** Presented to National Medical Care Management Committee
2.0	**07/12/2023:** Annual review with Optum Hematopoietic Stem Cell Transplantation, Chimeric Antigen Receptor T-cell Therapy, and Gene Therapy Expert Panel.
2.0	**07/31/2023:** Annual review. Approved by Optum Clinical Guideline Advisory Committee
2.0	**08/18/2023:** Annual review. Approved by Pharmacy &Therapeutics (P&T) Committee
2.0	**09/07/2023:** Annual review. Approved by Medical Technology Assessment Committee
2.0	**01/10/2024:** Interim revisions to add medical necessity criteria for Exagamglogene autotemcel (Casgevy™) and Lovotibeglogene autotemcel (Lyfgenia™) as treatments of sickle cell disease. Approved by Optum Clinical Guideline Advisory Committee
2.0	**01/17/2024:** Interim revisions to add medical necessity criteria for Exagamglogene autotemcel (Casgevy™) and Lovotibeglogene autotemcel (Lyfgenia™) as treatments of sickle cell disease. Approved by Pharmacy &Therapeutics (P&T) Committee
2.0	**02/01/2024:** Interim revisions to add medical necessity criteria for Exagamglogene autotemcel (Casgevy™) and Lovotibeglogene autotemcel (Lyfgenia™) as treatments of sickle cell disease. Approved by Medical Technology Assessment Committee
2.0	**03/19/2024:** Interim revision to add medical necessity criteria for Exagamglogene autotemcel (Casgevy™) as a treatment of β-thalassemia; added compliance with hydroxyurea or another prescribed treatment regimen to medical necessity criteria for Casgevy and Lyfgenia when used to treat patients with SCD. Approved by Optum Clinical Guideline Advisory Committee.
2.0	**04/04/2024:** Interim revision to add medical necessity criteria for Exagamglogene autotemcel (Casgevy™) as a treatment of β-thalassemia; added compliance with hydroxyurea or another prescribed treatment regimen to medical necessity criteria for Casgevy and Lyfgenia when used to treat patients with SCD. Approved by Medical Technology Assessment Committee.
2.0	**04/17/2024:** Interim revision to add medical necessity criteria for Exagamglogene autotemcel (Casgevy™) as a treatment of β-thalassemia; added compliance with hydroxyurea or another prescribed treatment regimen to medical necessity criteria for Casgevy and Lyfgenia when used to treat patients with SCD. Approved by Pharmacy & Therapeutics (P&T) Committee
2.0	**04/09/2024:** Interim revision to add medical necessity criteria for Atidarsagene autotemcel (Lenmeldy™) as a treatment of children with pre-symptomatic late infantile, pre-symptomatic early juvenile, or early symptomatic early juvenile metachromatic leukodystrophy. Approved by Optum Clinical Guideline Advisory Committee.
2.0	**04/17/2024:** Interim revision to add medical necessity criteria for Atidarsagene autotemcel (Lenmeldy™) as a treatment of children with pre-symptomatic late infantile, pre-symptomatic early juvenile, or early symptomatic early juvenile metachromatic leukodystrophy. Approved by Pharmacy &Therapeutics (P&T) Committee.
2.0	**05/02/2024:** Interim revision to add medical necessity criteria for Atidarsagene autotemcel (Lenmeldy™) as a treatment of children with pre-symptomatic late infantile, pre-symptomatic early juvenile, or early symptomatic early juvenile metachromatic leukodystrophy. Approved by Medical Technology Assessment Committee.

3.0	**05/16/2024:** Annual review by Optum Gene Therapy Expert Panel.
3.0	**08/09/2024:** Annual review; no substantive changes. Approved by Optum Clinical Guideline Advisory Committee.
3.0	**09/05/2024:** Approved by Medical Technology Assessment Committee.
3.0	**09/18/2024:** Approved by Pharmacy &Therapeutics (P&T) Committee.
4.0	**06/11/2025:** Annual review; added medical necessity criteria for Prademagene Zamikeracel (Zevaskyn™) indicated for the treatment of wounds in adult and pediatric patients with recessive dystrophic epidermolysis bullosa (RDEB). Approved by Optum Clinical Guideline Advisory Committee.
4.0	**07/10/2025:** Annual review; added medical necessity criteria for Prademagene Zamikeracel (Zevaskyn™) indicated for the treatment of wounds in adult and pediatric patients with recessive dystrophic epidermolysis bullosa (RDEB). Approved by Medical Technology Assessment Committee (MATC).
4.0	**07/16/2025:** Annual review; added medical necessity criteria for Prademagene Zamikeracel (Zevaskyn™) indicated for the treatment of wounds in adult and pediatric patients with recessive dystrophic epidermolysis bullosa (RDEB). Approved by Pharmacy and Therapeutics (P&T) Committee.
4.0	**09/10/2025:** Interim review; FDA-required update to the indication for elivaldogene autotemcel (Skysona®) due to new safety information on the increased risk of hematologic malignancy. Approved by Optum Clinical Guideline Advisory Committee.
4.0	**09/17/2025:** Interim review; FDA-required update to the indication for elivaldogene autotemcel (Skysona®) due to new safety information on the increased risk of hematologic malignancy. Approved by Pharmacy and Therapeutics (P&T) Committee.
4.0	**10/02/2025:** Interim review; FDA-required update to the indication for elivaldogene autotemcel (Skysona®) due to new safety information on the increased risk of hematologic malignancy. Approved by Medical Technology Assessment Committee (MTAC).
4.0	**10/08/2025:** Interim review; FDA-required update to the indication for elivaldogene autotemcel (Skysona®) due to new safety information on the increased risk of hematologic malignancy. Approved by Medicare Advantage Policy and Technology Assessment Committee (MAP TAC).
4.0	**03/09/2026:** Interim review; added medical necessity criteria for the indication of Wiskott-Aldrich Syndrome for etuvetidigene autotemcel (Waskyra™). Added genotype confirmation for Casgevy and Lyfgenia. Approved by Optum Clinical Guideline Advisory Committee.
4.0	**03/18/2026:** Interim review; added medical necessity criteria for the indication of Wiskott-Aldrich Syndrome for etuvetidigene autotemcel (Waskyra™). Added genotype confirmation for Casgevy and Lyfgenia. Approved by Pharmacy and Therapeutics (P&T) Committee.
4.0	**04/02/2026:** Interim review; added medical necessity criteria for the indication of Wiskott-Aldrich Syndrome for etuvetidigene autotemcel (Waskyra™). Added genotype confirmation for Casgevy and Lyfgenia. Placeholder for Medical Technology Assessment Committee (MTAC).
4.0	**04/08/2026:** Interim review; added medical necessity criteria for the indication of Wiskott-Aldrich Syndrome for etuvetidigene autotemcel (Waskyra™). Added genotype confirmation for Casgevy and Lyfgenia. Placeholder for Medicare Advantage Policy and Technology Assessment Committee (MAP TAC).