Optum

Gene therapy

Clinical guidelines

Effective Date: 09/07/2023

Table of Contents

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

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 may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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 on December 8, 2023.

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.

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) of non-transfusion-dependent thalassemia (NTDT) (Khandros & Kwiatkowski, 2019). The decision to initiate regular transfusions includes objective laboratory data as well as clinical findings.

Transfusions are recommended if the steady-state hemoglobin level is less than 7 g/dL. Poor growth, the development of frontal bossing or maxillary hyperplasia or other symptoms of anemia and ineffective erythropoiesis, even in the absence of severe anemia, should prompt initiation of transfusions. The goals of regular RBC 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. 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)

Treatment

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 ration, 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).

Two nonrandomized, open-label, single dose phase I/II studies (HGB-204, NCT01745120 and HGB-205, NCT02151526) were initiated in 2013 and enrolled 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 the 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.

- Transfusion dependence is defined as a minimum of eight transfusions or at least 100 ml per kilogram of body weight of packed red cells per year in the most recent two years.
- Documentation of one of the following genotypes confirmed by DNA analysis (beta-globin gene [HBB] sequencing):
    - Non-β0/β0 (Examples: β0/β+, βE/β0, and β+/β+)
    - β0/β0 (Examples: β0/β+ [IVS-I-110] and β+ (IVS-I-110]/β+ [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 and clearance obtained.
- 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.

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).

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:

- 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
- 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.

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)

Treatment

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 guide RNA included in the RNP complex enables CRISPR/Cas9 to make a precise DNA double-strand break at a critical transcription factor binding site (GATA1) in the erythroid specific enhancer region of the *BCL11A* gene. As a result of the editing, GATA1 binding is disrupted and BCL11A expression is reduced. This reduction in BCL11A expression conversely results in an increase in gamma-globin expression and downstream HbF formation.

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 cells. In patients with severe SCD, HbF expression reduces (HbS) concentration, preventing the red blood cells from sickling and addressing the underlying cause of the disease, thereby eliminating VOCs.

The 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 defines 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 the 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™) may be 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:

- 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 that 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
- Patient has not previously received gene therapy for the requested diagnosis

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.

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™) may be 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:

- 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 that the patient does not have more than two α-globin gene deletions
- Confirmative screening that 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
- 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.

References

ALD Alliance. ALD Alliance - Aidan Jack Seeger Foundation for Adrenoleukodystrophy. Accessed October 18, 2022.
Ali S, Mumtaz S, Shakir HA, et al. Current status of beta-thalassemia and its treatment strategies. Mol Genet Genomic Med. 2021 Dec;9(12):e1788. doi: 10.1002/mgg3.1788. Epub 2021 Nov 5. PMID: 34738740; PMCID: PMC8683628.

American Society of Gene and Cell Therapy : Gene Therapy 101: Different Approaches. Available at: https://patienteducation.asgct.org/gene-therapy-101/different-approaches Accessed October 7, 2022.

Bou-Fakhredin R, Motta I, Cappellini MD. Advancing the care of β-thalassaemia patients with novel therapies. Blood Transfus. 2022 Jan;20(1):78-88. doi: 10.2450/2021.0265-21. Epub 2021 Oct 21. PMID: 34694225; PMCID: PMC8796844.

Chou ST, Fasano RM. Management of Patients with Sickle Cell Disease Using Transfusion Therapy: Guidelines and Complications. Hematol Oncol Clin North Am. 2016 Jun;30(3):591-608. doi: 10.1016/j.hoc.2016.01.011. PMID: 27112998.

Eapen M, Brazauskas R, Walters MC, et al. Effect of donor type and conditioning regimen intensity on allogeneic transplantation outcomes in patients with sickle cell disease: a retrospective multicentre, cohort study. Lancet Haematol. 2019 Nov;6(11):e585-e596. doi: 10.1016/S2352-3026(19)30154-1. Epub 2019 Sep 5. PMID: 31495699; PMCID: PMC6813907.

Eichler F, Duncan C, Musolino PL, et al. Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy. N Engl J Med. 2017 Oct 26;377(17):1630-1638. doi: 10.1056/NEJMoa1700554. Epub 2017 Oct 4. PMID: 28976817; PMCID: PMC5708849.

European Medicines Agency. Multidisciplinary: Gene Therapy. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-gene-therapy Accessed October 7, 2022.

Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia. N Engl J Med. 2021 Jan 21;384(3):252-260. doi: 10.1056/NEJMoa2031054. Epub 2020 Dec 5. PMID: 33283989.

Gupta AO, Raymond G, Pierpont EI, et al. Treatment of cerebral adrenoleukodystrophy: allogeneic transplantation and lentiviral gene therapy. Expert Opin Biol Ther. 2022 Sep;22(9):1151-1162. doi: 10.1080/14712598.2022.2124857. Epub 2022 Sep 19. PMID: 36107226.

Huffnagel IC, Dijkgraaf MGW, Janssens GE, et al. Disease progression in women with X-linked adrenoleukodystrophy is slow. Orphanet J Rare Dis. 2019 Feb 7;14(1):30. doi: 10.1186/s13023-019-1008-6. PMID: 30732635; PMCID: PMC6367840.

Khandros E, Kwiatkoski JL. Beta Thalassemia: Monitoring and New Treatment Approaches. Hematol Oncol Clin N Am 2019;33:339-353.

Locatelli F, Thompson AA, Kwiatkowski JL, et al., Betibeglogene Autotemcel Gene Therapy for Non-β^0/β^0 Genotype β-Thalassemia. N Engl J Med. 2022 Feb 3;386(5):415-427. doi: 10.1056/NEJMoa2113206. Epub 2021 Dec 11. PMID: 34891223.

Moser HW, Mahmood A, Raymond GV. X-linked adrenoleukodystrophy. Nat Clin Pract Neurol. 2007 Mar;3(3):140-51. doi: 10.1038/ncpneuro0421. PMID: 17342190.

Moser AB, Fatemi A. Newborn Screening and Emerging Therapies for X-Linked Adrenoleukodystrophy. JAMA Neurol. 2018 Oct 1;75(10):1175-1176. doi: 10.1001/jamaneurol.2018.1585. PMID: 29946687.

Moser AB, Jones RO, Hubbard WC, et al. Newborn Screening for X-Linked Adrenoleukodystrophy. Int J Neonatal Screen. 2016 Dec;2(4):15. doi: 10.3390/ijns2040015. Epub 2016 Dec 6. PMID: 31467997; PMCID: PMC6715319.

Mettananda S, Higgs, DR. Molecular basis and genetic modifiers of thalassemia. Hematol Oncol Clin North Am 2018;32:177-91.

National Organization for Rare Disorders (NORD). Rare Disease Database: Beta Thalassemia. Available at: Beta Thalassemia - NORD (National Organization for Rare Disorders) (rarediseases.org). Accessed October 9, 2022.

Oikonomopoulou C, Goussetis E. HSCT remains the only cure for patients with transfusion-dependent thalassemia until gene therapy strategies are proven to be safe. Bone Marrow Transplant. 2021 Dec;56(12):2882-2888. doi: 10.1038/s41409-021-01461-0. Epub 2021 Sep 16. PMID: 34531544.

Pecker LH, Lanzkron S. Sickle Cell Disease. Ann Intern Med. 2021 Jan;174(1):ITC1-ITC16. doi: 10.7326/AITC202101190. Epub 2021 Jan 12. PMID: 33428443.

Strocchio L, Locatelli F. Hematopoietic Stem Cell Transplantation in Thalassemia. Hematol Oncol Clin North Am. 2018 Apr;32(2):317-328. doi: 10.1016/j.hoc.2017.11.011. PMID: 29458734.

Thompson AA, Walters MC, Kwiatkowski J, et al. Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia. N Engl J Med. 2018 Apr 19;378(16):1479-1493. doi: 10.1056/NEJMoa1705342. PMID: 29669226.

US Food and Drug Administration. CASGEVY™ Full Prescribing Information. Available at: Package Insert - CASGEVY (fda.gov). Accessed December 11, 2023.

US Food and Drug Administration. LYFGENIA™ Full Prescribing Information. Available at: Package Insert - LYFGENIA (fda.gov). Accessed December 11, 2023.

US Food and Drug Administration. SKYSONA® Full Prescribing Information. Available at: Package Insert – SKYSONA (fda.gov). Accessed October 17, 2022.

US Food and Drug Administration : What is gene therapy?. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy
Accessed October 7, 2022.

Zhu J, Eichler F, Biffi A, et al. The Changing Face of Adrenoleukodystrophy. Endocr Rev. 2020 Aug 1;41(4):577–93. doi: 10.1210/endrev/bnaa013. PMID: 32364223; PMCID: PMC7286618.

Review and approval history

Version	Date and description of activity
1.0	**11/3/2022:** New guideline. Approved by Medical Technology Assessment Committee
1.0	**12/19/2022:** Presented to National Medical Care Management Committee
2.0	**7/12/2023:** Annual review with Optum Hematopoietic Stem Cell Transplantation, Chimeric Antigen Receptor T-cell Therapy, and Gene Therapy Expert Panel.
2.0	**7/31/2023:** Annual review. Approved by Optum Clinical Guideline Advisory Committee
2.0	**8/18/2023:** Annual review. Approved by Pharmacy &Therapeutics (P&T) Committee
2.0	**9/7/2023:** Annual review. Approved by Medical Technology Assessment Committee
2.0	**1/10/2024:** 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	**1/17/2024:** 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	**2/1/2024:** 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