Healthy Blue

Medical Policy

Subject:	Gene Therapy for Cerebral Adrenoleukodystrophy		
Document #:	MED.00142	**Publish Date:**	01/03/2024
Status:	Reviewed	**Last Review Date:**	11/09/2023

Description/Scope

This document addresses gene replacement therapy for cerebral adrenoleukodystrophy (CALD), a rare and life-threatening hereditary neurological disorder. One gene therapy product, elivaldogene autotemcel (Skysona®), has been approved by the Food and Drug Administration (FDA) to treat individuals affected by CALD. Elivaldogene autotemcel is an autologous hematopoietic stem cell-based gene therapy that requires recipients to undergo hematopoietic stem cell (HSC) mobilization followed by apheresis to obtain CD34+ cells for elivaldogene autotemcel manufacturing, as well as administration of full myeloablative conditioning before infusion of elivaldogene autotemcel.

Note: For other information regarding adrenoleukodystrophy treatments, please see:

- CG-MED-68 Therapeutic Apheresis
- TRANS.00029 Hematopoietic Stem Cell Transplantation for Genetic Diseases and Aplastic Anemias

Position Statement

Medically Necessary:

A one-time infusion of elivaldogene autotemcel is considered **medically necessary** when **all** of the following criteria are met:

A. The individual is in the early stages of cerebral adrenoleukodystrophy (CALD), as confirmed by the following:
   1. Elevated very long chain fatty acid levels; **and**
   2. Confirmation of the presence of an *ABCD1* genetic mutation; **and**
   3. CALD-specific Neurological Function Scale (NFS) score of 0 or 1; **and**
   4. Active central nervous system (CNS) disease with demyelinating lesions demonstrated on brain gadolinium-enhanced MRI with Loes score between 0.5 and 9.0 on the 34-point scale; **and**

B. The individual is a candidate for an allogeneic hematopoietic cell transplantation, but ineligible due the absence of a donor*; **and**

C. The individual is 4 to 17 years of age; **and**

D. Absence of any clinically significant cardiovascular, hepatic, hematological, renal or pulmonary disease, or other disease or condition that poses a contraindication to the procedure, including myeloablative conditioning.

* Documentation that a suitable donor has not been identified, for example, a matched related donor or matched (HLA 8/8 or 7/8) unrelated donor.

Investigational and Not Medically Necessary:

Elivaldogene autotemcel is considered **investigational and not medically necessary** when the criteria above are not met, including for repeat infusions.

Rationale

Elivaldogene autotemcel (Skysona, bluebird bio, Inc., Somerville, MA) was approved by the U.S. Food and Drug Administration (FDA) on September 16, 2022 as a gene replacement therapy product for cerebral adrenoleukodystrophy (CALD). The FDA-approved indication is:

> …to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD). Early, active CALD refers to asymptomatic or mildly symptomatic (neurologic function score, NFS ≤ 1) boys who have gadolinium enhancement on brain magnetic resonance imaging (MRI) and Loes scores of 0.5-9.

FDA approval for elivaldogene autotemcel was based on the results of two unblinded case series involving subjects with early symptomatic CALD treated with elivaldogene autotemcel and followed for at least 24 months. Disease activity was defined as having detectable demyelinating lesions demonstrated on brain gadolinium-enhanced MRI, Loes score between 0.5, and 9, and NFS ≤ 1. Study 1 involved 32 subjects and Study 2 involved 35 subjects, and all subjects in both studies were male and aged 4 to 17 years. All subjects had elevated very long-chain fatty acid (VLCFA) levels and confirmed *ABCD1* mutations. The serious adverse event rate from initiation of therapy through last follow-up was 54%, and included febrile neutropenia (18%), pyrexia (18%), seizure (7%), myelodysplastic syndrome (MDS, 4%), pseudomonal bacteremia (3%), pancytopenia (3%), vascular device infection (3%), mucositis (3%), and vomiting (3%). At a minimum of 1 year, subjects reported experiencing seizure (15%) and MDS (6%). Additionally, 2 subjects had serious adverse reactions of pancytopenia for >1 year after treatment, requiring prolonged support with blood and platelet transfusions and growth factors. One of these subjects progressed to MDS. Platelet engraftment was achieved at a median of 29 days (range 14-108 days), but not achieved by 43 days in 13 of 63 subjects (21%). All subjects met criteria for neutrophil engraftment following treatment, but 7 of 67 subjects (10%) required G-CSF beyond 43 days, including 3 who required G-CSF for more than 3 months after treatment with elivaldogene autotemcel.

The populations of both Study 1 and Study 2 were compared to a retrospective population of elivaldogene autotemcel-untreated subjects with active early CALD (referred to as the "natural history control group" or "Study 3"). A post-hoc analysis investigating time from symptom onset to time of first major functional disability (MDF) or death in elivaldogene autotemcel-treated subjects (n=11, mean age at treatment 6 years [range 4-10]) vs. untreated subjects (n=7, mean age of 10 years at time of first NFS≥1[range 5-17]) indicated an advantage to elivaldogene autotemcel treatment, with estimated MDF-free survival at 24 months 72% vs. 43% (no p-value provided). Two (20%) elivaldogene autotemcel-treated subjects developed MDS and subsequently received allogeneic hematopoietic stem cell transplantation (HSCT). Another subject (10%) developed CALD symptoms with worsening MRI-detected brain lesions approximately 6 months following treatment with elivaldogene autotemcel and withdrew from the study to receive treatment with HSCT. That subject subsequently died of transplant-related complications.

Overall survival was determined in another post-hoc study comparing elivaldogene autotemcel-treated subjects from Study 1 and Study 2 to subjects from Study 3 plus data from a mixed prospective-retrospective allogeneic HSCT study (Study 4). This post-hoc comparison involved 61 elivaldogene autotemcel-treated subjects and 51 HSCT-treated subjects who were either HLA-matched (n=34) or HLA-mismatched (n=17). The Prescribing Information text states the study identified a difference in overall survival within the first 9 months following treatment in subjects who received HLA-mismatched HSCT vs. both elivaldogene autotemcel-treated subjects and HLA-matched HSCT. However, no data were provided to support this observation. The data presented by the FDA indicated no acute (≥ Grade II) or chronic graft vs. host disease (GVHD)-related adverse events in subjects treated with elivaldogene autotemcel. Finally, the FDA-presented data for 24 months reported that 7/36 (19%) evaluable elivaldogene autotemcel-treated subjects had a cerebral MRI Loes score increase of ≥ 6 points vs. 3/30 (10%) evaluable HSCT subjects, which was stated to be indicative of favorable results in the elivaldogene autotemcel-treated group (no p-value provided). The significance of this finding is unclear due to lack of statistical analysis and the loss of follow-up in the elivaldogene autotemcel group. Subjects in both Study 1 and Study 2 ware being enrolled in a long-term follow-up study.

In 2009 Cartier and colleagues reported the first in-vitro trial of gene replacement therapy with elivaldogene autotemcel in individuals with CALD. The study involved 2 male subjects with early-stage CALD with *ABCD1* mutations, progressive cerebral demyelination, adrenal insufficiency, and no HLA-matched donors or cord blood available for allogeneic hematopoietic stem cell transplantation (HSCT). The subjects were 7.5 (subject 1) and 7 (subject 2) years old at time of initial treatment. After a course of granulocyte colony-stimulating therapy and harvesting of peripheral blood mononuclear cells (PBMCs), both subjects underwent fully myeloablative conditioning before infusion with gene-edited autologous CD34+ cells. The cells were modified using a replication-defective HIV-1-derived lentiviral vector expressing wild-type *ABCD1* cDNA. Prior to infusion, 50% of subject 1's and 33% of subject 2's modified CD34+ cells were reported to have expressed adrenoleukodystrophy (ADL) protein production. Transfusion was uneventful in both subjects and hematopoietic recovery was noted in both at 13-14 days post-procedure and sustained throughout the 30-month follow-up period of the study. At 30 days post infusion, ALD expression was reported to be present in 23% and 25% of PBMCs in subject 1 and subject 2, respectively. At 9 months ALD expression decreased to 13% and 17%, respectively, which stabilized to 15% at 30 months and 14% at 24 months, respectively. VLCFA levels were reported to have reduced by 20% at 24 months in subject 1 and 28% in subject 2 at 20 months. Preoperative MRI demyelination scores of abnormal hyperintensity (Loes score) in several regions of the brain was at 2.25 out of 34 in subject 1. At 12 months post-transplant, gadolinium-enhanced MRI indicated complete resolution of demyelinating lesions, but demyelinating lesions continued to be present up to 14 months in the frontal white matter (demyelination score 6.75) and remained unchanged through the end of the 30 month study period. Preoperative MRI demyelination Loes scores of abnormal hyperintensity for subject 2 was 7, and was reported to have been more extensive than subject 1. At 9 months post-transfusion, gadolinium-enhanced MRI indicated complete resolution of demyelinating lesions, but minimal lesions reappeared at the anterior edge of the left parietal white matter at 16 months. This lesion was not detected in subsequent imaging. Demyelinating lesions continued to be present up to 16 months in the posterior parietal white matter. Demyelination of the auditory pathways disappeared completely, which the authors indicated as reversal of demyelination, and remained unchanged through the end of the 30-month study period. The final demyelination score at 30 months remained stable at 7 in subject 2. The authors noted that these results are similar to what is seen in subjects undergoing HSCT. Preoperatively, subject 1 had normal neurological examination and normal verbal intelligence (verbal intelligence quotient [VIQ] of 109), but moderate nonverbal performance deficit (non-verbal performance intelligence quotient [PIQ] of 99). At the end of the follow-up period verbal intelligence remained relatively unchanged (VIP=104) and an initial increase in nonverbal disability had stabilized at a PIQ of 74. Muscle

weakness developed on the right side of subject 1 at 7 months, which started to improve before nearly complete regression at 14 months. Subject 2 had normal motor and cognitive function preoperatively and remained stable after therapy (VIQ=103 and PIQ=111 at 20 months). At 14 months a visual field deficit appeared, which remained stable through the remainder of the trial. Plasma VLCFA levels were reduced by 39% in subject 1 at 24 months and by 38% in subject 2 at 20 months. As noted, these results are similar to those seen in individuals with CALD undergoing HSCT therapy, which is promising for individuals for whom such treatment is not an option. The authors concluded, "…lentiviral-mediated gene therapy of hematopoietic stem cells can provide clinical benefits in ALD."

The same group reported 36-month follow-up data on both subjects (Cartier, 2012). The report stated a stable percentage of corrected PBMCs between 10-13%. ALD expression in granulocytes, monocytes, and B and T lymphocytes ranged from 7-10% in subject 1 and from 12-14% in subject 2. ALD expression in bone marrow CD34+ cells was stable at 18% in both subjects. ALD protein expression was correlated with the mean number of integrated lentiviral copy per transduced CD34+ cell and PBMCs. In subject 1, no MRI evidence of cerebral demyelination progression was reported. Neurological examination remained normal as well, with the exception of a very moderate right triceps spasticity. This subject was reported to have received specialized education due to attention and executive deficits due to white matter lesions of the frontal lobes. In subject 2, as in subject 1, no MRI evidence of cerebral demyelination progression was reported at 36 months. However, dilation of the posterior part of the ventricles appeared at 16 months and progressed up to 30 months, indicating demyelination in the occipital white matter. The previously reported loss of visual field progressed through 30 months, which was associated with severe loss of visual acuity. No progression was reported between 30 and 36 months. No other neurological issues were reported for subject 2 since the last report at 24 months and they were performing normally in school with assistance for their visual deficits.

In 2017 Eichler published an interim analysis of the STARBEAM trial, an open-label, single-group phase 2-3 safety and efficacy trial. All subjects were male, had CALD-associated gadolinium-enhanced MRI lesions, a NFS score of 0 or 1, a Loes score of 0.5-9.0, and no HLA-matched donor available for HSCT. This interim analysis included 17 subjects between the ages of 4 and 13, out of a planned study population of 25 subjects. The gene replacement treatment protocol with elivaldogene autotemcel was identical to that described by Cartier (2009). Subjects were followed for an initial 2 years and offered enrollment in a 13-year extension study. At baseline, the mean NFS score was 0 and mean Loes score was 2. All subjects demonstrated post-treatment neutrophil and platelet engraftment. At the time of the interim analysis, the median follow-up time was 29.4 months and 16 of the 17 subjects could be evaluated for the primary endpoint. No toxic effects, deaths, graft failure, or instances of GVHD were reported. Integration site analysis indicated complete restitution of peripheral blood cells with polyclonal DNA, with stabilization at around 2 months. The range of CD14+ cells expressing ALD protein was 4.39 to 44.6% at 24 months. At the 23-month interim analysis point, 15 of the 17 subjects were alive and free of major functional disabilities, with an NFS score of 0 or 1. Neurologic progression was seen in 2 subjects, one who withdrew from the study and died of complications of a subsequent HSCT. The other subject experienced rapid neurological deterioration following gene replacement treatment, with MDF development by 9 months and death at 22 months due to viral infection complicated by rhabdomyolysis and acute organ failure. None of these adverse events were judged to be associated with elivaldogene autotemcel treatment. At 24 months, Loes score was reported to have stabilized in 12 of the 17 subjects (71%). The second subject described above had a Loes score of 7 at baseline and rapid MRI-detected disease progression after treatment during early engraftment. Their Loes score was 25 by 18 months. Gadolinium-enhanced MRI of CNS lesions was present in all subjects at baseline, but had resolved by 6 months in 16 subjects. Lesions were reported to have reemerged in 6 subjects at 12 months, with

resolution in 5. Additional reemergence of lesions was noted in 2 subjects at 24 months. In all subjects with reemergence, all subsequent lesions were much less extensive than the lesions detected at baseline. The authors concluded that the interim results of the STARBEAM trial suggest gene replacement therapy with elivaldogene autotemcel for CALD may be safe and effective, but additional follow-up is needed to fully assess the duration of response and long-term safety.

Bougnères (2021) reported long-term results on the 2 subjects described by Cartier (2009), with data from an additional 2 subjects who have not had their results previously published. The study population had a mean 8.8 years of follow-up. Gene therapy with elivaldogene autotemcel was conducted at 4.4 years of age in subject 3 and at 7 years of age in subject 4. The same treatment protocol described by Cartier (2009) were used for all subjects. Preoperatively, both subject 3 and subject 4 had normal or near-normal neurocognitive functions, similar to subjects 1 and 2. Only subject 3 remained neurologically and cognitively stable at 8.3 years post-treatment. In contrast, cognitive function declined at various rates in subjects 1, 2 and 4 at 9, 60 and 16 months, respectively. In subject 1 and 4, this was due to initially mild frontal syndrome. At age 16, almost 9 years after treatment, subject 1 had become unable to make sentences or dress alone and had poor intellectual performance with disordered behavior. In subject 4, major cognitive decline resulted in the inability to conduct further testing at 33 months. Measurements on the NFS were not well correlated to cognitive function. As noted previously, subject 2 experienced visual field loss at 20 months. In this report, the authors reported significant deterioration in NFS in this subject after 5 years post-treatment, with development of cortical blindness and severe ataxia. At 8.4 years, subject 1 retained good neurological function (NFS=1) with severe cognitive decline. Subject 4 experienced seizures, loss of spontaneous speech and urinary incontinence along with severe cognitive decline at 11.5 years. Gadolinium-enhanced MRI detection of demyelination disappeared from subjects 1, 2, and 3 at 12, 9 and 1.5 months post-treatment, respectively. In subject 4, enhancement on MRI disappeared at 4 months, reappeared at 16 months and persisted for 4.5 years before disappearing again at 5.5 years. The authors pointed out that both subject 1 and subject 4 experienced severe cognitive declines despite the absence of gadolinium-enhanced MRI detection of lesions. None of the 4 subjects had any treatment-related adverse events in the long term. Full results from this trial are pending.

Safety Concerns

Study of elivaldogene autotemcel (ClinicalTrials.gov NCT03852498) was placed on hold by the FDA in August 2021 after a subject developed MDS. In a press release by bluebird bio on August 9, 2021, they stated:

> The company received a reported Suspected Unexpected Serious Adverse Reaction (SUSAR) of myelodysplastic syndrome (MDS), that is likely mediated by Lenti-D lentiviral vector (LVV) insertion, in a patient who was treated with eli-cel, or Lenti-D drug product for CALD over one year ago in the Phase 3 ALD-104 study. Evidence currently available suggests that specific design features of Lenti-D LVV likely contributed to this event. The company has shared this information with the independent data monitoring committee of the study and the FDA has placed the eli-cel program on a clinical hold.

Another press release from June 9, 2022 also notes:

> Consistent with this known risk, two additional cases of MDS have subsequently been reported. All patients who received eli-cel in the clinical program continue to be closely monitored, per study

> protocols. […] Enrollment into studies of eli-cel is currently on hold with the FDA and follow-up of all patients continues, per protocol.

While the clinical hold by the FDA was lifted before granting elivaldogene autotemcel approval, these events raise serious concerns regarding the safety of elivaldogene autotemcel, and the potential for long term adverse events. The use of human autologous cells modified with the Lenti-D virus vector for the treatment of CALD has a limited track record and the risk for genotoxic effects is not well understood.

The FDA-approved prescribing information addresses this issue in a black box warning that states:

> Hematologic malignancy, including life-threatening cases of myelodysplastic syndrome, has occurred in patients treated with SKYSONA. The cancers appear to be the result of the SKYSONA lentiviral vector, Lenti-D, integration in proto-oncogenes. Monitor patients closely for evidence of malignancy through complete blood counts at least every 6 months and through assessments for evidence for clonal expansion or predominance at least twice in the first year and annually thereafter; consider bone marrow evaluations as clinically indicated.

In addition to insertional mutagenesis, augmenting mechanisms for leukemogenesis include transplant conditioning regimens, and expansion of preexisting premalignant clonal populations driven by regeneration of hematopoiesis with expansion of the autologous HSC population (Jones, 2021).

In 2022, Engelen and others published a consensus statement that included recommendations for the diagnosis and management of individuals with adrenoleukodystrophy. That document stated the following regarding the use of gene therapy for CALD:

> 17. Genetically transduced autologous stem cell transplantation (gene therapy) should be considered (if available) in boys if allogeneic donor options are poor.
>
> Allogeneic hematopoietic cell transplantation (HCT) is the standard treatment for cerebral ALD and can halt progression. Outcome is poor in advanced disease (Loes score >9 and/or neurologic function score >1).e14 In men, severe spinal cord disease (Expanded Disability Status Scale score >6) and bilateral internal capsule involvement are associated with poor survival.
>
> In boys, autologous hematopoietic stem cell transplantation after ex vivo lentiviral gene therapy has been studied as a safer alternative. Long-term safety data are not yet available. Currently, this therapy is not available for routine care. Treatment for boys or men with advanced disease or progressive lesions without gadolinium enhancement should only be considered after careful evaluation in experienced centers.

Conclusion

The current evidence addressing the clinical utility of elivaldogene autotemcel for the treatment of CALD is limited to the published results of two low-powered studies and unpublished data presented to the FDA. All of these studies have used similar criteria, which are reflected in the FDA approved indication, based on the natural history of early CALD and standard medical practice for the assessment and treatment of early CALD. All of the available studies

have involved male subjects under the age of 18, given that early CALD presents between 3 and 10 years (and rarely after 15 years of age), and exclusively impacts X-chromosome hemizygotes (boys with an XY chromosome makeup). Females (individuals with two X chromosomes) who are heterozygous for a pathogenic *ABCD1* mutation often develop a milder adrenomyeloneuropathy form of ALD symptoms during adulthood. Given that some ALD cases can spontaneously arrest, disease-modifying treatment is appropriate for affected individuals with evidence of central nervous system involvement on MRI who are early in their disease course (i.e., mild or no signs or symptoms). Identification of early CALD includes laboratory analysis for VLCFAs, confirmation of mutations in the *ABCD1* gene, assessment of clinical symptoms via the NFS tool, and brain imaging with gadolinium-enhanced MRI imaging to identify the presence of characteristic brain lesions. The current standard treatment for individuals with early CALD involves allogeneic HSCT with an appropriately matched donor. The benefits and risks of HSCT have been well studied and should be considered the first-line option for individuals with CALD when a suitable donor has been identified.

As noted above, the current data indicate significant risks to the use of elivaldogene autotemcel, including life-threatening cases of MDS, and those related to mobilization, apheresis, and myeloablative conditioning (similar to HSCT), as well as unclear long-term durability. However, given the rarity of CALD and the severity of outcomes for individuals affected with early CALD with no HSCT options, the available evidence suggests that treatment with elivaldogene autotemcel is likely to result in a net health benefit, including clinically significant delays in progression of symptoms, at least in the short term. While there is only limited data available to date, there is some indication that a delay in progression may have some durability, but long-term studies are needed to fully assess the clinical benefit of elivaldogene autotemcel. Nonetheless, the data appears to indicate that the use of elivaldogene autotemcel may provide a benefit well after individuals affected with early CALD could have reasonably been expected to survive. Based on the available data, the use of elivaldogene autotemcel for select individuals with CALD may be an acceptable option.

Background/Overview

Adrenoleukodystrophy (ALD) is an X-linked genetic disease caused by mutation of the adenosine triphosphate (ATP)-binding cassette (ABC), subfamily D, member 1 (*ABCD1*) gene which codes for the adrenoleukodystrophy protein (ADLP). Early childhood cerebral forms of CALD (called cerebral adrenoleukodystrophy) represents approximately 35 percent of all phenotypes in the group of conditions referred to as ALD. Disease phenotype does not correlate with the type of mutation, and different phenotypes can be seen within the same family. The result of the faulty gene is toxic buildup of VLCFAs, predominantly in the adrenal glands, brain, and spinal cord leading to loss of myelin sheath in the nerves and degeneration of function in the adrenal glands and central and peripheral nervous systems. Early (childhood) CALD presents between 3 and 10 years of age (peak 7 years), resulting in progressive neurological deterioration. Without treatment, rapid progression is common, with total disability in six months to two years, and death within 5 to 10 years of diagnosis. A combination of typical clinical features and markedly elevated VLCFA levels is sufficient to establish a preliminary diagnosis in most affected males, but a diagnosis is confirmed by genetic testing. Brain MRI testing should also be conducted to demonstrate demyelination in cerebral white matter. The natural history of CALD is characterized by rapid loss of neurological function and serious disability, followed by death. Spontaneously arrested ALD occurs in approximately 10 to 15 percent of ALD cases, characterized by an absence of symptom progression and lack of lesion growth or enhancement on sequential MRI. A minority of patients with arrested ALD eventually convert to progressive ALD.

Due to the X-linked nature of the disease, males (X-chromosome hemizygotes) are predominantly affected. Early symptoms of CALD may not be easily detected and may include adrenal insufficiency or behavioral problems. As the disease progresses, more severe symptoms arise, including vision and hearing problems/loss, seizures, swallowing problems, and loss of voluntary and involuntary motor function. Decline in intellectual abilities is also common. The 5-year survival rate is approximately 50% if untreated.

Prior to the FDA approval of elivaldogene autotemcel, the only available disease-modifying treatment for CALD was HSCT, which involves the transfer of blood stem cells from a genetically matched donor. Such treatment has been reported to provide stabilization of neurologic symptoms but has serious potential complications such as GVHD and graft failure, and matched donors are frequently unavailable. For individuals with CALD who undergo successful HSCT at an early stage of disease, five-year survival is greater than 90 percent. HSCT does not appear to affect the course of adrenal dysfunction in patients with ALD, so patients require ongoing monitoring for adrenal dysfunction, and treatment, if necessary. HSCT is not recommended in individuals without MRI evidence of cerebral involvement, given that approximately one-half of these individuals will remain free of cerebral disease. HCST is also not recommended in individuals with advanced disease given that available evidence suggests that HCST does not improve clinical outcomes in these individuals. Management of patients with advanced cerebral involvement is primarily supportive.

Recently the use of gene replacement therapy has been proposed for the treatment of CALD. Such treatment involves replacing or correcting a missing or faulty gene in the body's cells with the intention of restoring proper function. Missing or faulty DNA may be changed using genome editing, a group of technologies that allows genetic material to be added, removed, or altered from a cell. There are different approaches to gene therapy including replacing a mutated gene with a healthy gene, inactivating a malfunctioning mutated gene, or introducing a new gene.

To address CALD, bluebird bio, Inc. (Somerville, MA) has developed a new gene replacement therapy product, elivaldogene autotemcel (Skysona®). This product is composed of genetically modified autologous CD34+ cells that have been altered to include the wild-type *ABCD1* DNA. This product is custom manufactured for each recipient using their own hematopoietic stem cells, which are harvested after a period of treatment intended to increase the desired type of cells used in the process. Once the cells have been collected, the individual undergoes full myeloablative conditioning to eliminate their existing hematopoietic system with the intention of replacing it with the new modified cells. The modified cells are infused into the individual and are intended to engraft into the bone marrow and create new stem cells, some of those cells migrate to the nervous system and adrenal glands, where they are intended to produce functional ALDP to locally breakdown VLCFAs and stabilize the treated individual's condition. The result of this type of treatment is intended to be life-long, but robust long-term data are not available at this time. Individuals undergoing treatment with elivaldogene autotemcel require long-term, regular monitoring for treatment success and for the evaluation of potential adverse events. Like HCST, elivaldogene autotemcel does not treat or prevent adrenal insufficiency.

As noted earlier, elivaldogene autotemcel is an autologous hematopoietic stem cell-based gene therapy. This type of treatment requires a pre-treatment procedure to collect CD34+ cells for genetic manipulation. That procedure involves mobilization, apheresis, and myeloablative conditioning, which are addressed in the prescribing information:

Mobilization and Apheresis

- Patients are required to undergo HSC mobilization followed by apheresis to obtain CD34+ cells for product manufacturing. Weigh the patient prior to the first apheresis collection. Collect a minimum target number of CD34+ cells of 12×10^6 CD34+ cells/kg.
- A back-up collection of CD34+ cells of $\geq 1.5 \times 10^6$ CD34+ cells/kg (if collected by apheresis) or $\geq 1.0 \times 10^8$ TNC/kg (Total Nucleated Cells, if collected by bone marrow harvest) is required. Collect and cryopreserve these cells prior to initiating conditioning and infusion with SKYSONA. The back-up collection may be needed for rescue treatment if there is: 1) compromise of SKYSONA after initiation of conditioning and before SKYSONA infusion, 2) primary engraftment failure, or 3) loss of engraftment after infusion with SKYSONA.

Myeloablative and Lymphodepleting Conditioning

- Full myeloablative and lymphodepleting conditioning must be administered before infusion of SKYSONA. Consult prescribing information for the conditioning agents prior to treatment.
- Do not begin conditioning until SKYSONA has been received and stored at the treatment center and the availability of the back-up collection of CD34+ cells is confirmed. After completion of conditioning, allow a minimum of 48 hours of washout before SKYSONA infusion.

Definitions

Demyelinating lesions: Areas in nervous system tissue where the insulating myelin of the neurons breaks down, causing dysfunction of the effected tissue.

Very long chain fatty acid (VLCFA): A substance normally manufactured by the body's cells, including in the brain and central nervous system, which play an important part in cell function. In CALD, the mechanism by which healthy concentrations of VLCFAs is faulty, leading to higher than normal concentrations and disruptions in cell function.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

HCPCS	
C9399	Unclassified drugs or biologicals [when specified as elivaldogene autotemcel (Skysona)]
J3490	Unclassified drugs [when specified as elivaldogene autotemcel (Skysona)]
J3590	Unclassified biologics [when specified as elivaldogene autotemcel (Skysona)]

ICD-10 Diagnosis

E71.520	Childhood cerebral X-linked adrenoleukodystrophy

When services are Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

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Peer Reviewed Publications:

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2. Cartier N, Hacein-Bey-Abina S, Bartholomae CC, et al. Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy. Science. 2009; 326(5954):818-823.
3. Cartier N, Hacein-Bey-Abina S, Bartholomae CC, et al. Lentiviral hematopoietic cell gene therapy for X-linked adrenoleukodystrophy. Methods Enzymol. 2012; 507:187-198.
4. Eichler F, Duncan C, Musolino PL, et al. Hematopoietic stem-cell gene therapy for cerebral adrenoleukodystrophy. N Engl J Med. 2017; 377(17):1630-1638.
5. Jones RJ, DeBaun MR. Leukemia after gene therapy for sickle cell disease: insertional mutagenesis, busulfan, both, and neither. Blood. 2021; 138(11):942-947.
6. Lauer A, Speroni SL, Choi M, et al. Hematopoietic stem-cell gene therapy is associated with restored white matter microvascular function in cerebral adrenoleukodystrophy. Nat Commun. 2023;14(1):1900.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Bluebird Bio. Prescribing information for Skysona. https://www.bluebirdbio.com/-/media/bluebirdbio/Corporate%20COM/Files/Skysona/SKYSONA_Prescribing_Information.pdf. Accessed on November 14, 2023.
2. Engelen M, van Ballegoij WJC, Mallack EJ, et al. International Recommendations for the Diagnosis and Management of Patients With Adrenoleukodystrophy: A Consensus-Based Approach. Neurology. 2022; 99(21):940-951.
3. U.S. National Library of medicine. Clinicaltrials.gov. A clinical study to assess the efficacy and safety of gene therapy for the treatment of cerebral adrenoleukodystrophy (CALD). NCT03852498. Available at: https://clinicaltrials.gov/ct2/show/study/NCT03852498. Accessed on November 14, 2023.

Websites for Additional Information

1. National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center. X-linked cerebral adrenoleukodystrophy. https://rarediseases.info.nih.gov/diseases/9412/x-linked-cerebral-adrenoleukodystrophy. Last Updated: February 2023. Accessed on November 14, 2023.

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CALD
Cerebral adrenoleukodystrophy
Eli-cel
Elivaldogene autotemcel
Skysona

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale and References sections.
Revised	11/10/2022	MPTAC review. Revised note in Position Statement related to suitable donor. Updated References section.
New	09/26/2022	MPTAC review. Initial document development.
Preliminary Discussion	08/11/2022	MPTAC-Pre-FDA approval review.