Policy Number	**RX501.149**
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Elivaldogene autotemcel

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Elivaldogene autotemcel (Skysona®) **may be considered medically necessary** if ALL of the following criteria are met:

1. Individuals who are assigned male at birth and 4 to 17 years of age with early, active cerebral adrenoleukodystrophy (CALD), defined by the following:
    a. Elevated very long chain fatty acids (VLCFA) values, AND
    b. Active central nervous system disease established by central radiographic brain magnetic resonance imaging (MRI) demonstrating:
        i. Gadolinium enhancement (GdE+), AND
        ii. Loes score between 0.5 and 9 (inclusive) on the 34-point scale, AND
2. A neurologic function score (NFS) ≤ 1, AND
3. Individual does **NOT** have ANY of the following:
    a. History of prior gene therapy or allogenic hematopoietic stem cell transplant;
    b. Use of statins or Lorenzo's Oil;
    c. Hematological compromise as evidenced by:
        i. Peripheral blood absolute neutrophil count (ANC) count <1500 cells/ cubic millimeter (mm^3), and either:
            1. Platelet count <100,000 cells/mm^3, or
            2. Hemoglobin <10 gram per deciliter (g/dL);
    d. Hepatic compromise as evidenced by:
        i. Aspartate transaminase (AST) value > 2.5 times the upper limit of normal (ULN); OR
        ii. Alanine transaminase (ALT) value > 2.5 times the ULN; OR
        iii. Total bilirubin value > 3.0 milligram per deciliter (mg/dL), except if there is a diagnosis of Gilbert's Syndrome and the participant is otherwise stable;
    e. Baseline estimated glomerular filtration rate <70 milliliter per minute (mL/min)/1.73 square meter (m^2);
    f. Cardiac compromise as evidenced by left ventricular ejection fraction <40%;
    g. Positive for HIV, hepatitis B or C virus.

Repeat treatment of Elivaldogene autotemcel (Skysona®) **is considered experimental, investigational, and/or unproven.**

Elivaldogene autotemcel (Skysona®) **is considered experimental, investigational, and/or unproven** for all other indications.

Policy Guidelines

None.

Description

X-Linked Adrenoleukodystrophy (ALD, X-ALD)
X-linked adrenoleukodystrophy (ALD) is a rare genetic disorder that mainly affects the nervous system and adrenal glands, which sit atop the kidneys and produce hormones vital to proper health and development including cortisol and the sex hormones. In this disorder, the fatty covering or myelin that insulates nerves in the brain and spinal cord tends to deteriorate. The loss of myelin reduces the ability of the nerves to relay information to the brain; and damage to the outer layer of the adrenal glands causes a shortage of certain hormones.

Mutations in the *ABCD1* gene cause X-linked adrenoleukodystrophy. The *ABCD1* gene provides instructions for producing the adrenoleukodystrophy protein (ALDP), which is involved in transporting certain fat molecules called very long-chain fatty acids (VLCFAs) into peroxisomes. Peroxisomes are small sacs within cells that process many types of molecules, including VLCFAs.

ABCD1 gene mutations result in a shortage (deficiency) of ALDP. When this protein is lacking, the transport and subsequent breakdown of VLCFAs is disrupted, causing abnormally high levels of these fats in the body. The accumulation of VLCFAs may be toxic to the adrenal cortex and myelin. Research suggests that the accumulation of VLCFAs triggers an inflammatory response in the brain, which could lead to the breakdown of myelin. The destruction of these tissues leads to the signs and symptoms of X-linked adrenoleukodystrophy.

X-linked adrenoleukodystrophy is inherited in an X-linked pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes in each cell. In males (who have only one X chromosome), one altered copy of the *ABCD1* gene in each cell is sufficient to cause X-linked adrenoleukodystrophy. Additionally, affected males pass the altered gene to all their daughters but none of their sons.

Because females have two copies of the X chromosome, one altered copy of the *ABCD1* gene in each cell usually does not cause features of X-linked adrenoleukodystrophy that are as severe as those in affected males. Most females with one altered copy of the gene develop some health problems associated with this disorder. Additionally, affected females have a 50 percent chance of passing the altered gene to each of their children.

The signs and symptoms of X-linked adrenoleukodystrophy tend to appear at a later age in females than in males. Affected women usually develop features of the adrenomyeloneuropathy type.

The prevalence of ALD is estimated to be between 1:10,000 to 1:17,000 individuals in the general population, and occurs throughout the world in all ethnic groups.

There are different forms or subdivisions of ALD:

- Adrenomyeloneuropathy (AMN);
- Adult cerebral ALD;
- Childhood cerebral ALD; or
- Addison's-only ALD.

For the purposes of this policy, the focus is strictly on childhood cerebral ALD impacting males.

Signs and Symptoms of Childhood Cerebral ALD (CALD)

According to the National Organization for Rare Disorders (NORD) website, 35% of affected males develop neurological symptoms between three and ten years of age; and almost never occurs before approximately two and a half to three years of age. Normal healthy boys will suddenly start to regress. They may show symptoms including vision changes, hyperactivity and learning difficulties; some may have difficulty writing, behavioral changes, clumsiness, and difficulty understanding speech. If the disease spreads throughout the brain, symptoms grow worse, including blindness, deafness, seizures, loss of muscle control, and eventually a vegetative state or death, typically within 2-3 years from onset of neurological symptoms. (1)

Diagnosis

Some infants may be diagnosed through newborn screening. A positive result does not mean the infant has ALD; a repeat test must be done to confirm the diagnosis. A genetic test may be ordered to identify the specific gene mutation that causes ALD. Some states in the United States have included ALD testing as part of the newborn screening programs.

Following a confirmed diagnosis, magnetic resonance imaging (MRI) may be recommended to assess how ALD has affected the brain. Asymptomatic boys should be closely monitored for signs of cerebral disease. It is important to identify brain MRI changes as early as possible since individuals with early MRI changes prior to neurological symptoms have the best outcome when undergoing therapy. Treatment with hematopoietic stem cell transplantation should only be considered in boys with abnormal MRI changes who are not yet exhibiting neurological symptoms.

Changes noted on the MRI are scored using the ADL-MR severity scoring system, or Loes score. A severity score of 0 to 34 is calculated for each MR scan based on a point system derived from location and extent of involvement and the presence of focal and/or global atrophy. The primary neuroanatomic compartments involved by adrenoleukodystrophy include supratentorial white matter, the corpus callosum, the auditory and visual pathways, and major projection fibers such as the pyramidal tract and the frontopontine tract. These primary locations were subcompartmentalized to allow for more discrimination in the scoring system. Areas of less-frequent involvement, such as the cerebellum, basal ganglia, and anterior thalamus, were also included in the scoring system but were not further subdivided. (4)

Treatment

The current standard of care to stop progression of neurological symptoms is allogeneic hematopoietic stem cell transplantation (HSCT), particularly in young boys or adolescents with evidence of central nervous system involvement early in the course of the disease and have no neurological symptoms. Studies conducted over the last two decades have shown HSCT stops the progression of neurological disease in ALD, although it does not improve adrenal insufficiency. It is only effective in early stages of the disease.

Elivaldogene Autotemcel (Skysona®)
Elivaldogene autotemcel (Skysona) is a one-time gene therapy custom-designed to treat the underlying cause of cerebral adrenoleukodystrophy (CALD). Skysona uses ex-vivo transduction with the Lenti-D lentiviral vector (LVV) to add functional copies of the *ABCD1* gene into a patient's own hematopoietic stem cells (HSCs). The addition of the functional *ABCD1* gene allows patients to produce the ALD protein (ALDP), which can then participate in the local degradation of very long-chain fatty acids (VLCFAs). This degradation of VLCFAs is believed to slow or possibly prevent further inflammation and demyelination. (2)

Regulatory Status
In September 2022, the U.S. Food and Drug Administration (FDA) granted Accelerated Approval to Skysona® (elivaldogene autotemcel) (bluebird bio, Inc., Somerville, MA), to slow the progression of neurologic dysfunction in boys 4-17 years of age with early active cerebral adrenoleukodystrophy (CALD). As a condition of the Accelerated Approval, bluebird has agreed to provide confirmatory long-term clinical data to the FDA. They anticipate this will include data from the ongoing long-term follow-up study (LTF-304), which follows patients treated in clinical trials for 15 years, and from commercially treated patients. The Skysona Biologics License Application (BLA) was reviewed by the U.S. FDA under priority review, and bluebird received a rare pediatric priority review voucher upon approval. Skysona was previously granted Orphan Drug designation, Rare Pediatric Disease designation, and Breakthrough Therapy designation. (2, 3)

Rationale

This medical policy was developed in October 2022 and is based on the clinical studies provided to the U.S. Food and Drug Administration for approval. (3)

The safety and efficacy of Skysona were assessed in two 24-month, open-label, single-arm studies in patients with early, active cerebral x-linked adrenoleukodystrophy (CALD) as defined by Loes score between 0.5 and 9 (inclusive) and gadolinium enhancement (GdE+) on magnetic resonance imaging (MRI), as well as a neurologic function score (NFS) of ≤ 1, indicating limited changes in neurologic function. The NFS was used to evaluate 15 domains of neurological function with a maximum score of 25. A total NFS=0 indicates absence of neurologic dysfunction or asymptomatic disease. The patients enrolled and treated with Skysona (Study 1, N=32; Study 2, N=35) all had elevated very long chain fatty acid (VLCFA) levels and confirmed mutations in the *ABCD1* gene. Following completion of Study 1 and Study 2, patients enroll in a

subsequent and ongoing long-term follow-up study. The efficacy of Skysona was compared to an external untreated natural history control. Data for the Natural History Population in the retrospective natural history study (Study 3) was collected from existing medical records for patients with CALD. The Natural History Population had early, active disease at diagnosis, though gadolinium status was defined by either having a GdE+ MRI during the study or unknown GdE status and clinical course that suggested active disease.

Skysona Studies

Study 1 is complete, and Study 2 is ongoing at the time of product approval. In Study 1, patients were 47% White/Caucasian, 38% Hispanic, 3% Asian, 3% Black or African American, and 16% other races including mixed race. In Study 2, patients were 60% White/Caucasian, 14% Hispanic, 6% Black or African American, 6% other races including mixed race.

Mobilization and Apheresis

- G-CSF 10 µg/kg (median) for a minimum of 4 days
- Plerixafor 0.24 mg/kg for up to 3 days – optional in Study 1 (administered to 34% of patients) and required in Study 2

For all patients, one cycle of mobilization and apheresis and one to two apheresis collection days were sufficient to obtain the requisite number of cells needed for manufacturing.

Pre-treatment Myeloablative Conditioning

- Study 1: Busulfan dose median (min, max) 14 (11.2 to 16.8) mg/kg over 4 days
- Study 2: Busulfan dose median (min, max) 16.8 (12 to 21.2) mg/kg over 4 days

Pre-treatment Lymphodepletion

- Study 1: Cyclophosphamide dose median (min, max) 199 (151 to 213) mg/kg over 4 days
- Study 2: Fludarabine dose 180 mg/m2 over 6 days for 11 patients; 160 mg/m2 over 4 days (actual dose range 122 to 196 mg/m2) for 24 patients; (fludarabine dose decrease due to viral infections in the initial cohort)

Patients received seizure, hepatic veno-occlusive disease, anti-fungal, and antibiotic prophylaxis in accordance with institutional guidelines.

Skysona Administration

- All patients were administered SKYSONA as an intravenous infusion with a median (min, max) dose of 12 × 106 (5, 38.2) CD34+ cells/kg (N=67).

After Skysona Administration:

- G-CSF – optional in Study 1 (administered to 75% of patients) and required in Study 2 (beginning on Day 5)
- See below for engraftment information.

Platelet Engraftment Delay

Platelet engraftment was defined as 3 consecutive platelet values ≥ 20 × 109/L on different days and no platelet transfusions administered for 7 days immediately preceding and during the evaluation period. Platelet engraftment was not achieved by Day 43 after Skysona administration in 13 of 63 patients (21%). Patients treated with Skysona achieved platelet engraftment at median (min, max) Day 29 (14, 108) in clinical studies, including two patients treated with a thrombopoietin receptor agonist at the time engraftment criteria were met until 10 or 14 months after treatment with Skysona. One of the two had persistence of mild thrombocytopenia after discontinuation of the eltrombopag, and the other remained severely thrombocytopenic (platelet count < 50 × 109/L) until he was diagnosed with myelodysplastic syndrome approximately 2 years after Skysona administration.

Neutrophil Engraftment
Neutrophil engraftment was defined as achieving 3 consecutive absolute neutrophil counts (ANC) ≥ 0.5 × 109 cells/L (after initial post-infusion nadir) obtained on different days by Day 43 after Skysona infusion. While all patients met criteria for neutrophil engraftment following treatment with Skysona in clinical trials, 7 of 67 patients (10%) required G-CSF beyond Day 43, including 3 patients who required G-CSF more than 3 months after treatment with Skysona. In three other patients, G-CSF discontinuation was followed by a decrease in neutrophil count to < 0.5 × 109 cells/L occurring within 3 days and lasting for two to five weeks.

Comparison of Skysona with the Natural History of CALD
A post-hoc enrichment analysis in symptomatic patients compared time from onset of symptoms (NFS ≥ 1) to time to first major functional disability (MFD) or death (i.e., MFD-free survival) in Skysona treated and Natural History patients. The MFDs are defined as: loss of communication, cortical blindness, requirement for 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 initial NFS ≥ 1 or have had an event (MFD or death).

The 7 patients in the Natural History Population were a median (min, max) 9 (5, 15) years old at time of CALD diagnosis, and 10 (5, 17) years at time of first NFS ≥ 1. The median Loes score at diagnosis was 5 (2, 9). Four (57%) had a baseline brain MRI pattern of disease inclusive of parieto-occipital involvement, 2 (29%) had frontal disease (without parieto-occipital involvement) and 1 (14%) had isolated pyramidal tract disease. One (14%) had a baseline NFS=1 at diagnosis, and the remainder were asymptomatic (NFS=0) at diagnosis.

The symptomatic Skysona subpopulation (N=11) had baseline median (min, max) age at treatment of 6 (4, 10) years, age at first NFS ≥ 1 of 7 (4, 10) years, and a baseline Loes score of 2.5 (1, 9). Ten (91%) patients had a parieto-occipital pattern of disease on brain MRI and 1 (9%) had isolated pyramidal tract disease. At baseline, 2 (18%) patients had an NFS=1 and the remainder were asymptomatic (NFS=0) prior to treatment.

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. Kaplan-Meier (KM) estimated MFD-free survival at Month 24 from time of first NFS ≥ 1 were 72% (95% CI: 35%, 90%) for the symptomatic Skysona subpopulation and 43% (95% CI: 10%, 73%) for the Natural History Population. 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.

Isolated Pyramidal Tract Disease

Two untreated patients in Study 3 had early CALD with isolated pyramidal tract disease on brain MRI. Both remained asymptomatic for approximately 10 years following CALD diagnosis with first symptoms documented at 19 and 20 years of age. Ten patients with early, active pyramidal tract disease were treated with Skysona in Studies 1 and 2 and have only been followed a maximum of 77 months following treatment and to a maximum age at last follow-up of 15 years. Two (20%) Skysona-treated patients were diagnosed with myelodysplastic syndrome (MDS) and received allo-HSCT as treatment of the hematologic malignancy. One (10%) patient developed symptoms and worsening lesions on brain MRI approximately 6 months following treatment with Skysona and was withdrawn from the study to receive allo-HSCT at the investigator's discretion. He subsequently died of transplant-related causes.

Comparison of Skysona with Allogeneic Hematopoietic Stem Cell Transplant (allo-HSCT)

There were insufficient data to compare relative efficacy of Skysona to the standard of care, allogeneic hematopoietic stem cell transplant (allo-HSCT) in the treatment of CALD. However, while it does not inform the efficacy analysis, comparison of Skysona with an external allo-HSCT control (pooled from Study 3 and from a mixed prospective and retrospective allo-HSCT data collection study, Study 4) was performed for overall survival (OS) due to concerns about treatment-related toxicities. OS was analyzed as time-to-event Kaplan-Meier estimates comparing Skysona (entire efficacy population, N=61) to early, active allo-HSCT subpopulations by donor type: human leukocyte antigen (HLA)-Matched allo-HSCT Subpopulation (N=34) and HLA-Mismatched allo-HSCT Subpopulation (N=17). There were insufficient long-term data to compare OS beyond Month 24. However, a distinct difference in OS in the first 9 months following treatment was seen for the subpopulation who received allo-HSCT from an HLA-mismatched donor as compared to Skysona and allo-HSCT from an HLA-matched donor. While this analysis does not provide evidence of efficacy of Skysona, it does demonstrate a survival advantage of Skysona as compared to allo-HSCT from an HLA-mismatched donor, with early mortality in the HLA-mismatched allo-HSCT subpopulation largely attributed to allo-HSCT-related toxicities.

No patient experienced acute (≥Grade II) chronic graft versus host disease (GVHD) after Skysona treatment.

Post-treatment Brain MRI

At Month 24 following treatment with Skysona, 7/36 (19%) evaluable patients had a cerebral MRI Loes score increase of ≥ 6 points; 3/30 (10%) evaluable allo-HSCT patients had a cerebral MRI Loes score increase of ≥ 6 points.

Summary of Evidence

Based on the clinical studies provided to the U.S. Food and Drug Administration, elivaldogene autotemcel (Skysona®) may be considered medically necessary for select individuals ages 17 years or younger with early, active cerebral adrenoleukodystrophy (CALD) defined by the following: elevated very long chain fatty acids; and active central nervous system disease established by central radiographic brain magnetic resonance imaging demonstrating gadolinium enhancement and Loes score between 0.5 and 9 (inclusive) on the 34-point scale; and a neurologic function score ≤1 and the individual does not have any of the following: history of prior gene therapy or allogenic hematopoietic stem cell transplant; use of statins or Lorenzo's Oil; hematological compromise, hepatic compromise, baseline estimated glomerular filtration rate <70 milliliter per minute, cardiac compromise, or is positive for HIV, hepatitis B or C virus. Repeat treatment of Elivaldogene autotemcel (Skysona) is considered experimental, investigational, and/or unproven. Elivaldogene autotemcel (Skysona) is considered experimental, investigational, and/or unproven for all other indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	C9399

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. X-Linked Adrenoleukodystrophy. National Organization for Rare Disorders. Available at: <https://www.rarediseases.org>. Accessed October 11, 2022.
2. bluebird bio – bluebird bio receives FDA accelerated approval for SKYSONA® Gene Therapy for early, active cerebral adrenoleukodystrophy (CALD). Sept. 16, 2022. Available at: <https://www.investor.bluebirdbio.com>. Accessed October 11, 2022.
3. FDA – Skysona® highlights of prescribing information. U.S. Food and Drug Administration. Revised September 2022. Available at: <https://www.fda.gov>. Accessed October 11, 2022.

4. Loes DJ, Hite S, Moser H, et al. Adrenoleukodystrophy: A scoring method for brain MR observations. AM J Neuroadiol 15:1761-1766, Oct 1994. PMID 7847225

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
05/15/2024	Review only. No changes.
12/01/2023	Document updated. The following modification was made to Coverage: Changed from “Individuals aged 17 years or younger…” to “Individuals who are assigned male at birth and 4 to 17 years of age…”. No new references added.
03/01/2023	New medical document. Elivaldogene autotemcel (Skysona®) may be considered medically necessary for individuals ages 17 years or younger when the criteria noted in Coverage are met. Repeat treatment of Elivaldogene autotemcel (Skysona®) is considered experimental, investigational, and/or unproven. Elivaldogene autotemcel (Skysona®) is considered experimental, investigational, and/or unproven for all other indications.