BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

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| **EVIDENCE-BASED CRITERIA** | **ORIGINAL EFFECTIVE DATE: 12/01/22** |
| **SECTION: SPECIALTY MEDICAL DRUGS** | **LAST REVIEW DATE: 11/21/24** |
| | **CURRENT EFFECTIVE DATE: 11/21/24** |
| | **LAST CRITERIA REVISION DATE: 11/21/24** |
| **NEXT ANNUAL REVIEW DATE: 4TH QTR 2025** | **ARCHIVE DATE:** |

# GENE THERAPY FOR CEREBRAL ADRENOLEUKODYSTROPHY (CALD):

- **SKYSONA™ (elivaldogene autotemcel)**

**Non-Discrimination Statement is located at the end of this document.**

**Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.**

**This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.**

**The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.**

**The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.**

**State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.**

**Evidence-Based Criteria are subject to change as new information becomes available.**

**For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.**

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- **SKYSONA™ (elivaldogene autotemcel)**

**Criteria:**

**Refer to FDA website for current indications and dosage.**

- **Criteria for initial therapy:** Skysona (elivaldogene autotemcel) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with pediatric Neurologist or Hematologist

2. Individual is a biological male 4 to 17 years of age at the time of infusion

3. Individual has a confirmed diagnosis of early, active cerebral adrenoleukodystrophy (CALD) as indicated by **ALL** of the following:

   - Genetic test confirming mutation in the *ABCD1* gene
   - Laboratory evaluation documenting elevated very long chain fatty acid (VLCFA) levels
   - Asymptomatic or mildly symptomatic (NFS ≤ 1) (see Definitions section)
   - Recent brain MRI (within prior 6 months) demonstrates gadolinium enhancement of demyelinating lesions AND a Loes scores of 0.5-9 (see Definitions section)

4. Individual has completed **ALL** the following baseline tests:

   - Serologic tests for hepatitis B and C (HB surface Ag, anti-HB surface Ab, anti-HB core Ab, and hepatitis C antibody tests)
   - HIV test
   - Human T-lymphotropic (HTLV-1/HTLV-2) test

5. Individual meets **ALL** of the following:

   - Eligible for an allogeneic hematopoietic stem cell transplantation, but a potential HLA-matched related donor has not been identified or is unwilling to donate
   - Not taking HIV anti-retroviral medications for prophylaxis or plan to stop at least 1 month prior to mobilization
   - CALD is not secondary to head trauma

6. Individual does **NOT** have **ANY** of the following:

   - Estimated glomerular filtration rate less than 70 ml/min/1.73m$^2$ or creatine clearance is less than 50 ml/min
   - Cardiac, hematological or hepatic compromise (see Definitions section)
   - Active clinically significant infection, including but not limited to HIV, HTLV-1 virus, hepatitis B or C, bacteria, viral, fungal, parasitic infections
   - Prior gene therapy or is being considered for treatment with any other gene therapy

## GENE THERAPY FOR CEREBRAL ADRENOLEUKODYSTROPHY (CALD):
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- Prior allogenic hematopoietic stem cell transplant
- Immediate family member with a known or suspected Familial Cancer Syndrome (see Definitions section)

7. The Attestation for Skysona Treatment form (see below) has been signed by the physician (or designee)

**Approval duration:** One-time treatment per lifetime
The safety and effectiveness of repeat administration of Skysona (elivaldogene autotemcel) have not been evaluated.

**Approval Conditions**:
If an individual meets all coverage guideline criteria and is approved to receive treatment, the requesting provider attests and agrees to submit clinical outcomes data and information.

- Skysona (elivaldogene autotemcel) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any one or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.

### Attestations for Skysona Treatment

**Physician Name**: _____

**Individual Name:** _____ DOB**:** _____

- The Physician is responsible for filling out this form. This form may be completed by the physician requesting and administering Skysona or by the referring neurologist or hematologist who will resume follow-up care for cerebral adrenoleukodystrophy (CALD).
- All elements must be initialed, and the form must be signed by the Physician (or designee).

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- Incomplete forms will be returned to acquire missing information, initial, signature, or date.
- Return completed form to BCBSAZ.

**Physician Agreement:**
- Physician to initial by each element and date and sign to show willingness to participate.
- Documentation may include, but is not limited to, chart notes, laboratory test results, claims records, and/or other information.

Initials:

_____ I verify that the patient will be closely followed and monitored for progression of disease

_____ I agree to submit clinical outcomes data and information

Provider (or designee) Signature: _____

Date: _____

**Description:**

Adrenoleukodystrophy (ALD) is a rare, X-linked, metabolic disorder caused by a mutation in the adenosine triphosphate (ATP)-binding cassette, subfamily D, member 1 gene (ABCD1). Mutations in this gene results in the toxic buildup of very long-chain fatty acids (VLCFA) in plasma and all tissues, including the white matter of the brain, spinal cord and adrenal cortex. There are multiple phenotypes and onset of symptoms varies from mild to severe and progressive. Males are primarily affected but woman can be symptomatic later in life. Childhood cerebral ALD (CALD) is the most severe and neurogenerative form. Its onset is between 2.5 to 10 years of age with defects in cognition, decline in school performance and auditory impairment. It is rapidly progressive with mortality within 2 to 4 years after onset.

The incidence of ALD is 1 in 17,000 births and about 35% of the males with ALD will develop childhood CALD. The only treatment option for CALD has been hematopoietic stem cell transplants with varying levels of success. HLA-matched allogenic hematopoietic stem cell transplants (HSCT) are the most successful with the least complications. However, less than 30% have access to an HLA-matched donor. It is important to treat early in CALD, preferably asymptomatically, because once symptoms advance, treatment is ineffective. Newborn screening for ALD has been recommended and most states have implemented it. With regular MRI monitoring for changes in white matter, CALD can be detected early before symptoms develop.

Skysona is an autologous gene therapy which adds functional copies of the ABCD1 cDNA into patients' hematopoietic stem cells (HSCs) through transduction of autologous CD34+ cells with Lenti-D LVV. After

infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate into various cell types, including monocytes (CD14+) capable of producing functional ALDP. Functional ALDP can then participate in the local degradation of very long chain fatty acids (VLCFAs), which is believed to slow or possibly prevent further inflammation and demyelination.

Skysona is indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD). Early, active cerebral dystrophy 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. The indication is approved under accelerated approval based on 24-month Major Functional Disability (MFD)-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

**Limitations of Use:**

- Skysona does not prevent the development of or treat adrenal insufficiency due to adrenoleukodystrophy
- An immune response to Skysona may limit the persistence of descendent cells of Skysona, causing rapid loss of efficacy in patients with full deletions of the human adenosine triphosphate binding cassette, sub family D, member 1 (*ABCD1*) transgene.
- Skysona has not been studied in patients with CALD secondary to head trauma
- Given the risk of hematologic malignancy with Skysona, and unclear long-term durability and human adrenoleukodystrophy protein (ALDP) expression, careful consideration should be given to the appropriateness and timing of treatment for each boy, especially for boys with isolated pyramidal tract disease based on available treatment options since their clinical symptoms do not usually occur until adulthood

Elivaldogene autotemcel will be administered at qualified treatment centers (QTC) in the United States and requires an intensive four step process with additional monitoring after administration. Due to the complexity of stem-cell based gene therapy only available at QTCs, care coordination should be considered to assist the member when needed.

SKYSONA™ (elivaldogene autotemcel) Qualified Treatment Center Locator

- Step 1: Collection of blood stem cells through mobilization and apheresis. This process takes approximately one week. Granulocyte-colony stimulating factor (G-CSF) and plerixafor were used for mobilization.

- Step 2: Blood stem cells are sent to the manufacturing site and the functioning *ABCD1* complimentary DNA is attached to the stem cells to make Skysona. This step takes approximately 51-65 days.
- Step 3: The individual is hospitalized and myeloablative chemotherapy (busulfan) is administered.

- Step 4: Skysona is administered intravenously. The individual remains hospitalized during administration and for monitoring afterward for approximately 2 months.

**Definitions:**

Mobilization: first step in autologous stem cell transplants done to increase number of stem cells released in the blood; hematopoietic stem cell mobilization is done by administering granulocyte-colony stimulating factor (G-CSF) and plerixafor prior to autologous transplantations

Apheresis: process of removing peripheral blood mononuclear cells, specifically CD34+ cells for product manufacturing. For Skysona, these cells are sent to manufacturer to add functional copies of modified β-globin gene (HBB) to the stem cells to later be infused back into the patient

Myeloablative Conditioning: Administration of busulfan to destroy hematopoietic cells in the bone marrow which results in pancytopenia that is irreversible until administration of stem cells.

Cardiac Compromise: Left ventricular ejection fraction (LVEF) < 40%

Hematological Compromise:

- Peripheral blood absolute neutrophil count (ANC) count <1500 cells/ cubic millimeter ($mm^3$), and either
- Platelet count <100,000 cells/$mm^3$, or
- Hemoglobin <10 gram per deciliter (g/dL).
- Uncorrected bleeding disorder

Hepatic Compromise:

- Aspartate transaminase (AST) value > 2.5 × upper limit of normal (ULN)
- Alanine transaminase (ALT) value >2.5 × ULN
- Total bilirubin value >3.0 mg/dL, except if there is a diagnosis of Gilbert's Syndrome and the individual is otherwise stable

Familial Cancer Syndrome: Cancers including but not limited to hereditary breast and ovarian cancer syndrome, hereditary non-polyposis colorectal cancer syndrome, and familial adenomatous polyposis

Loes Score: The Loes score is a rating of the severity of abnormalities in the brain found on MRI. It ranges from 0 to 34, based on a point system derived from the location and extent of disease and the presence of atrophy in the brain, either localized to specific points or generally throughout the brain. A Loes score of 0.5 or less is classified as normal, while a Loes score of 14 or greater is considered severe. Stem cell transplants are generally not recommended for Loes scores greater than 9.

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Neurologic Function Scale (NFS) for CALD: 25-point scale used to evaluate the severity of gross neurologic dysfunction. The 6 most severe disabilities are loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement. These were classified as Major Functional Disabilities in the clinical trials.

| **Neurologic Function** | **NFS Score** |
|---|---|
| Hearing/Auditory processing problems | 1 |
| Aphasia/apraxia | 1 |
| Loss of communication | 3 |
| Vision Impairment | 1 |
| Cortical blindness | 2 |
| Swallowing dysfunctions | 2 |
| Tube feeding | 2 |
| Running difficulties | 1 |
| Walking difficulties/spasticity | 1 |
| Spastic gait (need assistance) | 2 |
| Wheelchair dependence | 2 |
| No voluntary movement | 3 |
| Episodes of incontinence | 1 |
| Total incontinence | 2 |
| Non-febrile seizures | 1 |
| **Possible Total** | **0-25** |

| **History:** | **Date:** | **Activity:** |
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| Pharmacy and Therapeutics Committee | 11/21/24 | Review with revisions: Criteria, Attestation, Description |
| Pharmacy and Therapeutics Committee | 11/16/23 | Review with revisions |
| Pharmacy and Therapeutics Committee | 12/01/22 | Approved Guideline |
| Clinical Pharmacist | 10/01/22 | Development |

**Coding:**

HCPCS: C9399, J3590

## GENE THERAPY FOR CEREBRAL ADRENOLEUKODYSTROPHY (CALD):
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**Resources:**

**Literature reviewed 11/21/24. We do not include marketing materials, poster boards and non-published literature in our review.**

1. Eichler F, Duncan C, Musolino PL, et al. Hematopoietic stem-cell gene therapy for cerebral adrenoleukodystrophy. *N Engl J Med*. 2017;377(17):1530-1538.

2. Engelen M. Management and prognosis of X-linked adrenoleukodystrophy. In: UpToDate, Patterson MC, Hahn S, Dashe JF, et al. (Eds). UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated July 26, 2024. Accessed September 5, 2024.

3. Mallack EJ, Turk BR, Yan H, et al. MRI surveillance of boys with X-linked adrenoleukodystrophy identified by newborn screening: Meta-analysis and consensus guidelines. *J Inherit Metab Dis*. 2021;44(3):728-739.

4. Skysona (elivaldogene autotemcel) prescribing information, revised by bluebird bio, Inc. 04/2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 5, 2024.

5. Wanders RJA, Engelen M. Clinical features, evaluation, and diagnosis of X-linked adrenoleukodystrophy. In: UpToDate, Patterson MC, Hahn S, Dashe JF, et al. (Eds). UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated March 19, 2024. Accessed September 5, 2024.

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**Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.**

**If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html**