


# PHARMACY / MEDICAL POLICY – 5.01.634

## Gene Therapies for Cerebral Adrenoleukodystrophy

Effective Date:	June 1, 2023	RELATED MEDICAL POLICIES:	None
Last Revised:	May 9, 2023		
Replaces:	N/A		

Select a hyperlink below to be directed to that section.

- [POLICY CRITERIA](#) | [DOCUMENTATION REQUIREMENTS](#) | [CODING](#)
- [RELATED INFORMATION](#) | [EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

 Clicking this icon returns you to the hyperlinks menu above.

### Introduction

Adrenoleukodystrophy (ALD) is a rare genetic condition caused by a mutation in the *ABCD1* gene on the X chromosome. Childhood cerebral ALD (CALD) is the most severe form of ALD. Boys with CALD typically start to show symptoms between 3 and 10 years of age, which can include learning disabilities, hearing loss, vision problems, body weakness, and seizures. Within 2-3 years, symptoms can progress to severe disability. This policy discusses when the use of Skysona® may be considered medically necessary.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

### Policy Coverage Criteria

Drug	Medical Necessity
<b>Skysona® (elivaldogene autotemcel) IV</b>	<b>Skysona® (elivaldogene autotemcel) may be considered medically necessary for treatment of adrenoleukodystrophy when the diagnosis is confirmed by an adenosine triphosphate</b>

Drug	Medical Necessity
	<p><b>binding cassette, sub family D member 1 (ABCD1) gene mutation and elevated very long chain fatty acid (VLCFA) levels when the following criteria are met:</b></p> <ul style="list-style-type: none"> <li>• Individual is 4 to 17 years of age</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Individual was assigned male at birth</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Individual has early, active disease as defined by ALL the following: <ul style="list-style-type: none"> <li>○ Neurologic function score (NFS) less than or equal to 1</li> <li>○ Gadolinium enhancement on central radiographic review of brain magnetic resonance imaging (MRI)</li> <li>○ Loes score between 0.5 and 9 on the 34-point scale</li> </ul> </li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Individual is eligible for an allogeneic hematopoietic stem cell transplant (HSCT)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Individual is unable to receive an allogeneic HSCT because no matched sibling donor is available</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• The member has not received a prior allogeneic HSCT</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Individual has not received Skysona® or any other gene therapy previously</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Use is prescribed by or in consultation with a hematologist or neurologist</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Use is limited to a one-time infusion</li> </ul>

Drug	Investigational
<p><b>Skysona® (elivaldogene autotemcel)</b></p>	<p><b>All other uses of Skysona® (elivaldogene autotemcel) for conditions not outlined in this policy are considered investigational.</b></p>



Drug	Investigational
	Repeat treatment with Skysona® (elivaldogene autotemcel) is considered investigational.

Length of Approval	
Approval	Criteria
Initial authorization	Skysona® (elivaldogene autotemcel) may be approved as a one-time infusion
Re-authorization criteria	Future re-authorization of Skysona® (elivaldogene autotemcel) beyond a one-time infusion is considered investigational.

Documentation Requirements
<p>The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:</p> <ul style="list-style-type: none"> <li>Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history</li> </ul>

## Coding

Code	Description
<b>HCPCS</b>	
J3590	Unclassified biologics (Skysona®)

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## Related Information

### Benefit Application

Skysona® (elivaldogene autotemcel) is managed through the medical benefit.



## Loes Magnetic Resonance Imaging (MRI) Severity Scale Scoring

Each region is given a score of 0 for normal, 0.5 for unilateral involvement, and 1 for bilateral involvement or atrophy. The maximum score is 34.

- Parieto-occipital white matter (maximum 4)
- Anterior temporal white matter (maximum 4)
- Frontal white matter (maximum 4)
  - Periventricular
  - Central
  - Subcortical
  - Local atrophy
- Corpus callosum (maximum 5)
  - Splenium
  - Genu
  - Splenium atrophy
  - Genu atrophy
- Global atrophy (maximum 4)
  - Mild
  - Moderate
  - Severe
  - Brainstem
- Visual pathway (maximum 4)
  - Optic radiation
  - Meyer's loop
  - Lateral geniculate body
  - Optic tract
- Auditory pathway (maximum 4)
  - Medial geniculate body
  - Brachium of inferior colliculus
  - Lateral lemniscus
  - Pons
- Cerebellum (maximum 2)
  - White matter
  - Atrophy
- Projection fibers (maximum 2)
  - Internal capsule





- Brain stem

## Neurologic Function Score (NFS)

Neurologic function is measured by cerebral adrenoleukodystrophy (CALD)-specific NFS, a 25-point scale (0 to 25) used to evaluate the severity of gross neurologic dysfunction by scoring 15 disabilities across multiple domains. A score of "0" denotes absence of clinical signs of cerebral disease. The 6 most severe disabilities listed on the NFS are loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement. These disabilities were judged to be of particular significance because they severely compromise a patient's ability to function independently.

NFS Component	NFS Score
Hearing/auditory processing problems	1
Aphasia/apraxia	1
<b>Loss of communication</b>	<b>3</b>
Vision impairment	1
<b>Cortical blindness</b>	<b>2</b>
Swallowing dysfunctions	2
<b>Tube feeding</b>	<b>2</b>
Running difficulties	1
Walking difficulties/spasticity	1
Spastic gait (need assistance)	2
<b>Wheelchair dependence</b>	<b>2</b>
<b>No voluntary movement</b>	<b>3</b>
Episodes of incontinence	1
<b>Total incontinence</b>	<b>2</b>
Non-febrile seizures	1

## Evidence Review



## Summary of Evidence

### Skysona® (elivaldogene autotemcel)

Skysona® is intended to be a one-time gene therapy and is designed to treat the underlying cause of cerebral adrenoleukodystrophy (CALD). The therapy uses ex vivo transduction with the Lenti-D lentiviral vector to add functional copies of the *ABCD1* gene into a individual's own hematopoietic stem cells (HSCs). The added gene allows individuals to produce adrenoleukodystrophy protein (ALDP) to help break down very-long-chain fatty acids (VLCFAs) and slow or possibly prevent further inflammation and demyelination. The administration of Skysona® is complex and requires specialized care. Both open-label, single-arm studies, ALD-102 and ALD-104, enrolled individuals with early, active CALD, evidenced by elevated VLCFA values and confirmed *ABCD1* mutations, a Loes score between 0.5 and 9, and gadolinium enhancement (GdE+) on MRI of demyelinating lesions. Additionally, participants were also required to have an NFS of  $\leq 1$ , indicating limited changes in neurologic function. In both trials, individuals were monitored for the six major functional disabilities (MFDs) associated with CALD progression that could emerge, including loss of communication, cortical blindness, requirement of tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement. 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 (ALD-101) was collected from existing medical records for individuals with CALD. The natural history population had early, active disease at diagnosis, although gadolinium status was defined by either having a GdE+ MRI during the study or unknown GdE status and clinical course that suggested active disease. A post hoc enrichment analysis in symptomatic individuals assessed MFD-free survival from onset of symptoms (NFS  $\geq 1$ ) in Skysona®-treated (n = 11) and untreated individuals (natural history population; n = 7). The seven individuals in the natural history cohort had a median age of 9 years (range, 5–15 years) at the time of CALD diagnosis and a median age of 10 years (range, 5–17 years) at time of first NFS  $\geq 1$ . The median Loes score at the time of diagnosis was 5 (range, 2–9). One individual (14%) had a baseline NFS of 1 at the time of CALD diagnosis, and the remaining six individuals (86%) were asymptomatic (NFS = 0) at the time of diagnosis. In the Skysona®-treated group, the 11 symptomatic individuals had a baseline median age of 6 years (range, 4–10 years) at the time of treatment, a median age of 7 years (range, 4–10 years) at time of first NFS  $\geq 1$ , and a baseline Loes score of 2.5 (range, 1–9). At baseline, two individuals (18%) had an NFS score of 1 and the remaining nine individuals (82%) were asymptomatic (NFS = 0) prior to treatment. Skysona®-treated individuals had an estimated 72% (95% CI: 35%, 90%) likelihood of MFD-free survival at 24 months from the time of first NFS  $\geq 1$ , whereas untreated individuals had an estimated 43% (95% CI: 10%, 73%) likelihood of MFD-free survival. The FDA's accelerated approval of Skysona® is based on 24-



month MFD-free survival. The clinical trial data were insufficient to compare the relative efficacy of Skysona® to that of hematopoietic stem cell transplantation (HSCT) for the treatment of CALD. However, due to concerns about treatment-related toxicities, Skysona® was compared with an external HSCT control (pooled from ALD-101 and from a mixed prospective and retrospective HSCT data collection study [ALD-103]) in regard to overall survival (OS), although this comparison did not inform the efficacy analysis. Overall survival was analyzed as time-to-event Kaplan-Meier estimates comparing Skysona® (entire efficacy population, N = 61) to early, active HSCT subpopulations by donor type: human leukocyte antigen (HLA)-matched HSCT subpopulation (n = 34) and HLA-mismatched HSCT subpopulation (n = 17). In the first 9 months following treatment, individuals who received Skysona® and individuals who received HSCT from an HLA-matched donor had higher OS compared with the subpopulation who received HSCT from an HLA-mismatched donor. At 24 months from the start of treatment with Skysona®, 7 of 36 (19%) evaluable individuals had a cerebral MRI Loes score increase of  $\geq 6$  points. In comparison, 3 of 30 (10%) evaluable HSCT individuals had a cerebral MRI Loes score increase of  $\geq 6$  points. The most common non-laboratory adverse reactions in individuals treated with Skysona® included mucositis, nausea, vomiting, febrile neutropenia, alopecia, decreased appetite, abdominal pain, constipation, pyrexia, diarrhea, headache, and rash (all 20% or more). The most common grade 3/4 laboratory abnormalities included leukopenia, lymphopenia, thrombocytopenia, neutropenia, anemia, and hypokalemia (all 40% or more). The label carries a boxed warning for hematologic malignancy.

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## History

Date	Comments
06/01/23	New policy, approved May 9, 2023. Added Skysona (elivaldogene autotemcel) coverage criteria. HCPCS code J3590 added for Skysona.

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