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PHARMACY / MEDICAL POLICY – 5.01.634

Gene Therapies for Cerebral Adrenoleukodystrophy

BCBSA Ref. Policy: 5.01.45

Effective Date:	May 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Apr. 21, 2025	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

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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
Skysona (elivaldogene autotemcel) IV	**Skysona (elivaldogene autotemcel) may be considered medically necessary for treatment of adrenoleukodystrophy**

Drug	Medical Necessity

	when the diagnosis is confirmed by an adenosine triphosphate 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:
	• The individual is aged 4 to 17 years
	AND
	• Was assigned male at birth
	AND
	• Has early, active disease as defined by ALL the following:
	  ○ Neurologic function score (NFS) less than or equal to 1
	  ○ Gadolinium enhancement on central radiographic review of brain magnetic resonance imaging (MRI)
	  ○ Loes score between 0.5 and 9 on the 34-point scale
	AND
	• Is eligible for an allogeneic hematopoietic stem cell transplant (HSCT)
	AND
	• Is unable to receive an allogeneic HSCT because no matched sibling donor is available
	AND
	• Has not received a prior allogeneic HSCT
	AND
	• Has not received Skysona or any other gene therapy previously
	AND
	• Use is prescribed by or in consultation with a hematologist or neurologist
	AND
	• Use is limited to a one-time infusion

Drug	Investigational
Skysona (elivaldogene autotemcel)	**All other uses of Skysona (elivaldogene autotemcel) for conditions not outlined in this policy are considered investigational.** **Repeat treatment with Skysona (elivaldogene autotemcel) is considered investigational.**

Drug	Investigational
	The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for Skysona (elivaldogene autotemcel) may be approved up to 12 months.** **All other reviews for 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
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: • Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

Code	Description
HCPCS	
J3590	Unclassified biologics (use to report: Skysona)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Benefit Application

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

Loes Magentic 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

Table 1: 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 individual's ability to function independently.

NFS Component	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

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 ≤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 ≥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 ≥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 ≥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 ≥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 ≥6 points. In comparison, 3 of 30 (10%) evaluable HSCT individuals had a cerebral MRI Loes score increase of ≥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.

International Recommendations for the Diagnosis and Management of Individuals with Adrenoleukodystrophy

Three international centers of excellence for adrenoleukodystrophy (ALD; Amsterdam UMC, Massachusetts General Hospital, and Kennedy Krieger Institute) aided by health consultancy agency Adelphi Values constituted a multi-disciplinary panel comprising of pediatric neurologists, endocrinologists, metabolic specialists, hematopoietic cell transplant experts, radiologists, laboratory scientists and individual advocacy groups to develop best-practice recommendations for diagnosis, clinical surveillance, and treatment of ALD using a consensus-based modified Delphi approach. The panel received financial support of Bluebird Bio, SwanBio Therapeutics, and Minoryx. The panel recommendations for treatment of cerebral adrenoleukodystrophy (CALD) are as follows:

- "Transplantation eligibility should be determined by an ALD transplantation expert.

- Eligibility criteria are not exclusive. In general, boys are considered eligible for transplantation when they have demyelination with gadolinium enhancement (MR severity score (Loes score) ≤9) and a neurological function score of 0 or 1; adult men when they have demyelinating lesions with gadolinium enhancement and no or few neurocognitive impairment.
- Genetically transduced autologous stem cell transplantation (gene therapy) should be considered (if available) in boys if allogeneic donor options are poor."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in **Table 2**.

Table 2: Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02698579[a]	Long-term Follow-up of Participants With Cerebral Adrenoleukodystrophy Who Were Treated With Lenti-D Drug Product	64	Aug 2038
NCT06224413[a]	A Study of Participants With Cerebral Adrenoleukodystrophy (CALD) Treated With Elivaldogene Autotemcel	120	Dec 2047
NCT05939232	Registry of X-linked Adrenoleukodystrophy	200	Dec 2028
Ongoing			
NCT03852498[a]	A Clinical Study to Assess the Efficacy and Safety of Gene Therapy for the Treatment of Cerebral Adrenoleukodystrophy (CALD)	35	July 2023

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

The Food and Drug Administration (FDA) has requested Bluebird Bio to conduct 2 post-marketing studies to verify the clinical benefit. These are

- Study 1: Follow all subjects who received elivaldogene autotemcel in Studies ALD-102 and ALD-104 to assess event-free survival (i.e., alive without major functional disability [MFD] or need for hematopoietic stem cell transplant [HSCT]) for a minimum of 10 years following administration of elivaldogene autotemcel. Timeline for final protocol submission is January 31, 2023, for interim clinical study report submission: July 31, 2027 and final study report submission: July 31, 2032.
- Study 2: Investigate event-free survival for at least five years post-treatment in 24 boys with more advanced early active, CALD [(based on baseline Loes scores and Neurologic Function Score (NFS)] who will be newly treated with elivaldogene autotemcel. Timeline for final protocol submission: January 31, 2023, study fully enrolled by: June 30, 2033, study completion date: June 30, 2038 and final study report submission: December 31, 2038.

References

1. Skysona Prescribing Information. bluebird bio, Cambridge, MA. Revised April 2024.
2. Bluebird bio. Skysona launch call. September 19, 2022. https://investor.bluebirdbio.com/events/event-details/skysonar-launch-call Accessed April 6, 2025.
3. Chiesa R, et al. Variables affecting outcomes after allogeneic hematopoietic stem cell transplant for cerebral adrenoleukodystrophy. Blood Adv. 2022;6(5):1512-1524. doi:10.1182/bloodadvances.2021005294
4. Eichler F, et al. Hematopoietic stem-cell gene therapy for cerebral adrenoleukodystrophy. N Engl J Med. 2017;377(17):1630-1638. doi:10.1056/NEJMoa1700554
5. National Institute of Health National Institute of Neurological Disorders and Stroke. Adrenoleukodystrophy. Updated September 19, 2022. **https://www.ninds.nih.gov/health-information/disorders/adrenoleukodystrophy** Accessed April 6, 2025.
6. National Organization for Rare Disorders (NORD). X-linked adrenoleukodystrophy. Last updated November 13, 2019. https://rarediseases.org/rare-diseases/adrenoleukodystrophy/ Accessed April 6, 2025.
7. Peters C, et al. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999 [published correction appears in Blood. 2004 Dec 15;104(13):3857]. Blood. 2004;104(3):881-888. doi:10.1182/blood-2003-10-3402
8. Raymond GV, et al. Survival and functional outcomes in boys with cerebral adrenoleukodystrophy with and without hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2019;25(3):538-548. doi:10.1016/j.bbmt.2018.09.036
9. Raymond GV, et al. X-Linked Adrenoleukodystrophy. In: Adam MP, et al., eds. GeneReviews [Internet]. University of Washington, Seattle; 1993-2022. Published March 26, 1999. Updated February 15, 2018. **https://www.ncbi.nlm.nih.gov/books/NBK1315/** Accessed April 6, 2025.
10. U.S. Food and Drug Administration. Cellular, Tissue, and Gene Therapies Advisory Committee. June 9–10, 2022 Meeting Announcement. **https://www.fda.gov/advisory-committees/advisory-committee-calendar/cellular-tissue-and-gene-therapies-advisory-committee-june-9-10-2022-meeting-announcement-06092022** Accessed April 6, 2025.

11. Loes DJ, Hite S, Moser H, et al. Adrenoleukodystrophy: a scoring method for brain MR observations. AJNR Am J Neuroradiol 1994;15(9):1761-1766.

12. Moser HW, Loes DJ, Melhem ER, et al. X-linked adrenoleukodystrophy: overview and prognosis as a function of age and brain magnetic resonance imaging abnormality: a study involving 372 patients. *Neuropediatrics*. 2000;31:227-39.

13. Moser HW. Adrenoleukodystrophy: phenotype, genetics, pathogenesis and therapy. Brain. Aug 1997; 120 (Pt 8): 1485-508. PMID 9278636

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

15. Loes DJ, Hite S, Moser H, et al. Adrenoleukodystrophy: a scoring method for brain MR observations. AJNR Am J Neuroradiol. Oct 1994; 15(9): 1761-6. PMID 7847225

16. Moser HW, Raymond GV, Dubey P. Adrenoleukodystrophy: new approaches to a neurodegenerative disease. JAMA. Dec 28 2005; 294(24): 3131-4. PMID 16380594

17. 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. May 2021; 44(3): 728-739. PMID 33373467

18. Loes DJ, Fatemi A, Melhem ER, et al. Analysis of MRI patterns aids prediction of progression in X-linked adrenoleukodystrophy. Neurology. Aug 12 2003; 61(3): 369-74. PMID 12913200

19. Melhem ER, Loes DJ, Georgiades CS, et al. X-linked adrenoleukodystrophy: the role of contrast-enhanced MR imaging in predicting disease progression. AJNR Am J Neuroradiol. May 2000; 21(5): 839-44. PMID 10815658

20. Peters C, Charnas LR, Tan Y, et al. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999. Blood. Aug 01 2004; 104(3): 881-8. PMID 15073029

21. Shapiro E, Krivit W, Lockman L, et al. Long-term effect of bone-marrow transplantation for childhood-onset cerebral X-linked adrenoleukodystrophy. Lancet. Aug 26 2000; 356(9231): 713-8. PMID 11085690

22. Mosser J, Douar AM, Sarde CO, et al. Putative X-linked adrenoleukodystrophy gene shares unexpected homology with ABC transporters. Nature. Feb 25 1993; 361(6414): 726-30. PMID 8441467

23. Executive Summary: X-linked adrenoleukodystrophy (X-ALD) to the Recommended Uniform Screening Panel. Available at https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/x-ald-exsum.pdf. Accessed April 6, 2025.

24. Hubbard WC, Moser AB, Liu AC, et al. Newborn screening for X-linked adrenoleukodystrophy (X-ALD): validation of a combined liquid chromatography-tandem mass spectrometric (LC-MS/MS) method. Mol Genet Metab. Jul 2009; 97(3): 212-20. PMID 19423374

25. Raymond GV, Jones RO, Moser AB. Newborn screening for adrenoleukodystrophy: implications for therapy. Mol Diagn Ther. 2007; 11(6): 381-4. PMID 18078355

26. Kemper AR, Brosco J, Comeau AM, et al. Newborn screening for X-linked adrenoleukodystrophy: evidence summary and advisory committee recommendation. Genet Med. Jan 2017; 19(1): 121-126. PMID 27337030

27. Miller WP, Rothman SM, Nascene D, et al. Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. Blood. Aug 18 2011; 118(7): 1971-8. PMID 21586746

28. Aubourg P, Blanche S, Jambaqué I, et al. Reversal of early neurologic and neuroradiologic manifestations of X-linked adrenoleukodystrophy by bone marrow transplantation. N Engl J Med. Jun 28 1990; 322(26): 1860-6. PMID 2348839

29. Engelen M, Kemp S, de Visser M, et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Orphanet J Rare Dis. Aug 13 2012; 7: 51. PMID 22889154

30. Raymond GV, Aubourg P, Paker A, et al. Survival and Functional Outcomes in Boys with Cerebral Adrenoleukodystrophy with and without Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. Mar 2019; 25(3): 538-548. PMID 30292747

31. Summary Basis for Regulatory Action for Elivaldogene Autotemcel. Available at https://www.fda.gov/media/162098/download. Accessed April 6, 2025.
32. Mahmood A, Dubey P, Moser HW, et al. X-linked adrenoleukodystrophy: therapeutic approaches to distinct phenotypes. Pediatr Transplant. Dec 2005; 9 Suppl 7: 55-62. PMID 16305618
33. Kühl JS, Kupper J, Baqué H, et al. Potential Risks to Stable Long-term Outcome of Allogeneic Hematopoietic Stem Cell Transplantation for Children With Cerebral X-linked Adrenoleukodystrophy. JAMA Netw Open. Jul 06 2018; 1(3): e180769. PMID 30646031
34. 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. Nov 22 2022; 99(21): 940-951. PMID 36175155

History

Date	Comments
06/01/23	New policy, approved May 9, 2023. Added Skysona (elivaldogene autotemcel) coverage criteria. HCPCS code J3590 added for Skysona.
09/01/24	Annual Review, approved August 26, 2024. No changes to policy statements.
05/01/25	Annual Review, approved April 21, 2025. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.