Molina Clinical Policy
Skysona (elivaldogene autotemcel): Policy No. 424

Last Approval: 12/11/2024
Next Review Due By: October 2025

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

This policy addresses the use of Skysona (elivaldogene autotemcel) for the treatment of cerebral adrenoleukodystrophy.

Adrenoleukodystrophy (ALD) is a rare, inherited metabolic storage disease caused by a mutation in the ABCD1 gene that affects production and /or function of the ALD protein (ALDP). Dysfunctional ALDP protein results in the buildup of toxic, very long-chain fatty acids (VLCFA) in the brain and spinal cord. Myelin, the protective covering of nerve cells in the brain, gradually deteriorate due to the accumulation of VLCFA in the white matter of the brain and spinal cord. Accumulation of VLCFA also occurs in the adrenal cortex causing adrenal issues. As ALD is an X-linked condition, the disease is significantly more severe in males. Affected females may exhibit spinal cord -related symptoms in adulthood (Gupta et al. 2022). There are three major manifestations of ALD in males: adrenal insufficiency, cerebral inflammatory demyelination (referred to as cerebral ALD or CALD), and axonal myeloneuropathy. ALD is the most common peroxisomal disorder affecting both males and females with an estimated birth incidence of about 1/14,700. Approximately 35% to 40% of males may develop rapidly progressive inflammatory cerebral demyelination peaking between ages 3 to 10 years (Turk et al. 2020).

Cerebral ALD (CALD) is the most severe form of ALD, with an onset in childhood, predominantly affecting males between the ages of 4 and 10 years old (median age 7). Symptoms include attention deficit hyperactivity disorder, progressive cognitive and behavioral problems, adrenal impairment, and distinctive MRI (Magnetic Resonance Imaging) abnormalities (Gupta el. 2022). Early diagnosis of CALD is critical because the outcome of treatment varies depending on the clinical stage of the disease. Nearly half of patients who do not receive treatment die within five years of symptom onset. ALD newborn screening is a crucial component of early diagnosis and, subsequent treatment for ALD. In the United States, newborn screening for ALD was added to the Recommended Universal Screening Panel in February 2016 and is available in almost all states (HRSA 2024). Plasma VLCFA levels and an ABCD1 gene mutation analysis is diagnostically conclusive for ALD.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been the only effective treatment option to stabilize disease progression by halting cerebral demyelination. Allo-HSCT should be performed at the early stage of cerebral involvement, prior to onset of neurological symptoms and before advanced brain disease occurs. However, allo-HSCT has a substantial risk of serious complications including death, particularly in patients who do not have a matched sibling donor. Gene therapy may provide a treatment option for patients who do not have a matched, related donor for allo-HSCT. Skysona (elivaldogene autotemcel) is a one-time gene treatment intended to stabilize neurologic function and address the underlying cause of this neurodegenerative disease. According to the manufacturer, Bluebird bio, eli-cel provides an alternative to allo-HSCT for the more than 70% of patients diagnosed with CALD who lack a matched sibling donor.

Skysona (elivaldogene autotemcel; eli-cel) adds functional copies of the ABCD1 gene into a patient's own hematopoietic stem cells using a lentiviral vector to transduce cells ex vivo and return the cells to the patient. The addition of a functional ABCD1 gene allows patients to produce ALDP, which aids in the breakdown of VLCFAs. The expression of ALDP and the effects of eli-cel are anticipated to last a lifetime. The purpose of eli-cel treatment is to halt the course of CALD and, accordingly, to preserve as much neurological function as possible, including motor

function and communicative capacity. Most significantly, eli-cel does not require donor HSCs. Skysona does not treat or prevent adrenal insufficiency.

Although Skysona is a one-time gene therapy, a treatment course consists of multiple phases: 1) mobilization and apheresis to collect CD34+ cells for manufacturing, 2) myeloablative and lymphodepleting conditioning, and 3) eli-cel infusion, with a minimum of 48-hour washout between conditioning and Skysona infusion. FDA approval included a **black box warning** for hematologic malignancy, including life-threatening cases of myelodysplastic syndrome and acute myeloid leukemia, which has developed in patients treated with eli-cel in clinical studies. Additional changes and considerations for prescribing clinicians are available from the FDA prescribing information (2024).

Skysona was granted accelerated approval by the FDA for the treatment of early, active CALD in patients without a human leukocyte antigen matched donor on September 16, 2022. Skysona is indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active CALD. Early, active CALD refers to asymptomatic or mildly symptomatic (neurologic function score, NFS ≤ 1) boys who have gadolinium enhancement on brain MRI and Loes scores of 0.5-9. The approval was 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 a confirmatory trial(s).

COVERAGE POLICY

All Gene Therapy requests require Molina Medical Director review.

Skysona (eli-cel) for the treatment of cerebral adrenoleukodystrophy (CALD) may be **considered medically necessary** when **ALL** the following clinical criteria with documentation are met:

1. A diagnosis of CALD is established by genetic (ABCD1 mutation analysis) and biochemical (VLCFA analysis) testing

2. Member is ≥ 4 years and ≤ 17 years at the time of infusion

3. Early active CALD documented with brain MRI demonstrating:
   a. Loes score between 0.5 and 9 (inclusive) on the 34-point scale
   b. Gadolinium enhancement on MRI of demyelinating lesions
   c. Neurologic function score, NFS ≤ 1 (asymptomatic or mildly symptomatic)

4. Clinical documentation and recent relevant evaluation, labs, and workup establishing eligibility for requested Skysona gene therapy must include the following:
   a. Member is clinically stable and eligible for an allogeneic HSCT, but a human leukocyte antigen matched related HSC donor is not available
   b. Adequate and stable renal, hepatic, and cardiac function as evidenced by recent evaluation and laboratory workup. Members with **ANY** of the following labs do **not** meet criteria:
      i. Hematological compromise as indicated by:
         a. Peripheral blood absolute neutrophil count < 1500 cells/mm^3, or
         b. Platelet count < 100,000 cells/mm^3, or
         c. Hemoglobin < 10 g/dL
      ii. Hepatic compromise defined by:
         a. Aspartate transaminase (AST) value > 2.5 X upper limit of normal (ULN)
         b. Alanine transaminase (ALT) value > 2.5 X ULN
         c. Total bilirubin value > 3.0 mg/dL, except if there is a diagnosis of Gilbert's Syndrome and the participant is otherwise stable
      iii. Renal compromise as evidenced by abnormal renal function (actual or calculated creatinine clearance < 50 mL/min)
      iv. Cardiac compromise as evidenced by left ventricular ejection fraction < 40%
   c. A negative serology test for HIV, hepatitis B or C virus, or human T lymphotropic virus 1 (HTLV-1)
      Exception: The following patients are *not* excluded from treatment: 1) Received vaccination against hepatitis B (hepatitis B surface antibody-positive) who are negative for other markers of prior hepatitis B infection [e.g., negative for hepatitis B core antibody (Ab)],

2) Past exposure to HBV (HBcAb positive and/or HBeAb positive) who have a negative test for HBV DNA, and 3) positive for anti-hepatitis C antibody are eligible if they have a negative HCV viral load.

d. Absence of clinically significant uncontrolled, active bacterial, viral, fungal, parasitic, or prion associated infection
e. Member has not received, nor is being considered, for other gene therapy or investigational cellular therapy
f. No prior allogeneic transplant
g. Females of childbearing potential and males capable of fathering a child: Member has been counseled on the use of effective contraception during treatment (from start of mobilization through at least 6 months after administration of eli-cel) AND advised of the risks associated with conditioning agents
h. Females of childbearing potential must not be pregnant or breastfeeding, AND must have a documented negative serum pregnancy test within the past 30 days
NOTE: A negative serum pregnancy test must be confirmed prior to the start of mobilization and re-confirmed prior to conditioning procedures and before eli-cel administration.

5. No known hypersensitivity to protamine sulfate

6. No contraindications to ANY of the following:
   a. Granulocyte colony-stimulating factor or plerixafor during the mobilization of hematopoietic stem cells
   b. Busulfan or fludarabine, including known hypersensitivity to the active substances or to any of the excipients in their formulations

7. No condition(s) that render MRI studies unfeasible (e.g., allergies to anesthetics or contrast agents)

8. No family history of an immediate family member with a known or suspected Familial Cancer Syndrome

CONTINUATION OF THERAPY

The safety and efficacy of repeat treatment has not been studied and is currently not supported by any compendia nor indicated in the current FDA approved labeling. Requests for reauthorization or beyond one dose is considered experimental and will not be authorized.

LIMITATIONS AND EXCLUSIONS

The following are considered **experimental, investigational, and unproven** based on insufficient evidence:
1. Any indications other than those listed above
2. Prior treatment with any form of HSCT, eli-cel, or other gene therapy

The following are key considerations:
1. Patients with whole gene deletions of the ABCD1 gene have experienced an immune response to Skysona and rapid loss of efficacy
2. Consideration should be given to the timing of Skysona therapy in those with isolated pyramidal tract disease. Patients with this isolated finding typically have much later disease onset

DURATION OF APPROVAL: Duration sufficient for **ONE** single course of treatment

PRESCRIBER REQUIREMENTS: Prescribed by, or in consultation with, a board-certified neurologist, pediatric metabolic specialist or pediatric neurogeneticist with experience in ALD treatment or transplantation

QUANTITY LIMITATIONS: ONE (1) single treatment course of Skysona per lifetime. Additional infusions of Skysona will not be authorized.

ADMINISTRATION:
1. Skysona is a provider-administered therapy to be administered in a Qualified Treatment Center by an ALD transplantation expert or physician(s) with experience in HSCT and in the treatment of patients with neurological disorders.
2. Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

SUMMARY OF MEDICAL EVIDENCE

The biological license application (BLA) for Skysona (eli-cel) was supported by the phase 2/3 STARBEAM study (ALD-102) (n=32) and phase 3 ALD-104 study (n=23), which evaluated the efficacy and safety of eli-cel in patients with early, active CALD. Enrollment is complete and all patients have been treated in both studies; **follow-up in ALD-104 is ongoing.**

Interim results published by Eichler et al. (2017) from study ALD-102 (NCT01896102) indicate eli-cel gene therapy for the treatment of CALD is at least as effective as conventional allogenic hematopoietic stem cell transplant. The absence of graft-versus-host disease (GVHD) indicates that the procedure may be safer than allogeneic transplant. The interim paper reported data on the 17 patients who completed 24-months of follow-up by 2017. The median age of this population at enrollment was 6 years (range: 4 to 13 years). All patients had a baseline CALD-specific neurologic function scale score of 0. The median baseline Loes score was 2.0 (range, 1.0 to 7.5). The median follow-up time for this initial sample of 17 patients at the time of data analysis was 29.4 months.

At follow up, 88% (15 of 17) patients were alive, with minimal clinical symptoms, 1 patient died from disease progression during pre-transplantation conditioning and 1 patient was withdrawn from the study and died from complications of a subsequent allogeneic transplantation. In the 15 remaining patients, no GVHD was observed. Fourteen of these 15 patients had a NFS score of 0 or 1, which indicates no or minimal clinical symptoms; and 12 of the 15 patients had a stable Loes score, indicating no progression of the lesion. Gadolinium enhancement, which was present at baseline in all the patients, was absent in all 15 patients by 6-months post-transplant. A few patients experienced re-emergence of gadolinium enhancement at various time points (including 2 patients at month 24), but the enhancement was less extensive than the gadolinium enhancement that was present at baseline.

Unpublished **STARBEAM study (ALD-102)** data has been reported on clinical trials.gov. This study enrolled 32 patients up to 17 years of age with early-stage CALD, treated with a single infusion of eli-cel after undergoing myeloablative conditioning with busulfan and cyclophosphamide. Early-stage CALD was defined as an MRI-based Loes score between 0.5 and 9 (inclusive), gadolinium enhancement on MRI of demyelinating lesions, and a NFS of ≤ 1, indicating limited changes in neurologic function. Patients were excluded from the study if they had a willing and available human leukocyte antigen matched sibling HSC donor. The median age at Skysona infusion was 6.0 years, 100% of patients were males. The median (min, max) Loes score at baseline was 2.00 (range: 1.0-9.0). Of the 32 patients, 31 had an NFS of 0 and one had an NFS of 1 at baseline.

The **primary efficacy endpoint** for the STARBEAM Study is the absence of major functional disabilities (MFDs) at 24 months after transplantation. MFDs correspond to severe disabilities thought to have a profound impact on a patient's ability to function independently including loss of ability to communicate, cortical blindness, need for tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement. At 24 months, 90.6% (29/32) of ALD-102 patients met the primary endpoint of MFD-free survival. Two participants withdrew at investigator discretion and 1 participant experienced rapid disease progression, MFD, and death.

The **secondary efficacy endpoint** of the study was the progression of cerebral disease. This is evaluated by gadolinium enhancement on brain MRI (which is an indicator of neuroinflammation) and by the Neurologic Function Score (NFS). The NFS is a scoring system that is used to evaluate the severity of clinical deficits by scoring 15 symptoms across multiple domains. The number of participants with a change in NFS score up to month 24 was 4 out of 30 evaluable participants. The report did not specify if these four experienced a loss or gain of neurologic function. The percentage of patients (n=30) demonstrating resolution of gadolinium positivity on MRI at month 24 was 86.7%. Twenty-four participants were analyzed for time to sustained resolution of gadolinium positivity on MRI. The median was 77 days with a range of 25 to 551 days. Overall survival at 24 months was reported to be 96.7%. All patients that completed ALD-102 enrolled for long-term follow-up in the LTF-304 study.

The safety profile of Skysona was also evaluated with regard to side-effects and genome integration analysis of the

gene. Myelodysplastic syndrome, viral cystitis, pancytopenia, and vomiting have all been linked to eli-cel in clinical trials. In the 55 patients who received eli-cel in clinical studies (ALD-102/LTF-304 and ALD-104), there were no reports of GVHD, graft failure or rejection, transplant-related mortality, or replication competent lentivirus in the patients who received eli-cel in clinical studies (ALD-102, ALD-104, LTF-304).

Phase 3 Studies

ALD-104 (NCT03852498) is an ***ongoing*** phase 3 study, which has completed enrollment and treatment of all patients. This study is designed to assess the efficacy and safety of eli-cel after myeloablative conditioning using busulfan and fludarabine in patients with CALD (a different chemotherapy conditioning regimen than used in ALD-102). Unpublished **study data from (ALD-104)** was reported on clinical trials.gov, last updated May 24, 2024. There were 35 participants in the study at a mean age of 7 years.

The **primary efficacy endpoint** was the proportion of patients alive and free of the 6 MFDs at month 24. Results posted ahead of peer reviewed publication show 85.7% of participants achieved this endpoint. All participants (100%) achieved neutrophil engraftment following eli-cel infusion, the primary safety endpoint. A **secondary endpoint** was the number of participants who achieved stable NFS scores at 24 months. A total of 33 out of 35 (94.3%) had stable NFS scores at 24 months.

Lund et al. (2024) reported a case follow-up from ALD-104 notable for a secondary failure. The patient had initial resolution of MRI enhancements, but 6 months after therapy the vector copy number dropped. Nine months after therapy, polyclonal antibodies arose. The antibodies demonstrated reactivity at the peroxisome where the new gene product is known to be localized and carries out its function. The patient had a whole gene deletion, and it is suspected that immunogenicity may have arisen due to the lack of prior exposure to the ABCD1 protein.

Phase 4 Long-Term Follow-up

LTF-304 (NCT02698579) is a multi-center long-term follow-up study that includes approximately 60 patients who have received eli-cel for CALD and completed two years of follow-up in ALD-102 or ALD-104. The participants will be followed for an additional 13 years, for a total of 15 years after drug product infusion. No investigational pharmaceutical product will be administered during this study (Estimated Study Completion Date: May 2037).

National and Specialty Organizations

American Academy of Neurology
International Recommendations for the Diagnosis and Management of Patients with Adrenoleukodystrophy: a Consensus-Based Approach (2022)

A consensus-based, modified Delphi method was utilized by 28 international ALD specialists to establish best-practice recommendations for the diagnosis, clinical monitoring, and treatment of ALD patients. The following is a summary of the notable recommendations reaching consensus

- '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.'

The guidelines further noted:

- The gold standard is genetic testing (ABCD1 analysis), with the detection of a known pathogenic ABCD1 variant confirming the diagnosis of ALD in both men and women. Plasma C26:0-lysophosphatidylcholine (C26:0-lysoPC) has superior diagnostic performance in biochemical testing. In the absence of these other options, fasting plasma VLCFAs (C26:0; C26:0/C22:0; C24:0/C22:0) should be obtained.
- The standard treatment for CALD is allo-HCT, which can halt progression. In advanced disease (Loes score > 9 and/or Neurological Function Score > 1), the outcome is poor. Severe spinal cord disease (Expanded Disability Status Scale score > 6) and bilateral internal capsule involvement are associated with a poor chance of survival in men.

- Autologous HCT following ex vivo lentiviral gene therapy has been studied as a safer alternative for males. However, there are no published data on the long-term safety of this treatment, and it is currently not available in routine care. The treatment of boys or men with severe disease or progressive lesions in the absence of gadolinium enhancement should only be considered in experienced treatment centers

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

Code	Description
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
96415	Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure)

HCPCS (Healthcare Common Procedure Coding System)

Code	Description
C9399	Unclassified drugs or biologicals (hospital outpatient use only) [when specified as Skysona (elivaldogene autotemcel)]
J3590	Unclassified biologics [when specified as Skysona (elivaldogene autotemcel)]
Billing Units: When billing for **Skysona** using the NOC (Not Otherwise Classified) codes **C9399** or **J3590**, the units billed should be represented as each patient **(EA).**	

AVAILABLE DOSAGE FORMS: Skysona is supplied in 1 or 2 infusion bags containing a frozen suspension of genetically modified autologous cells, enriched for CD34+ cells. A single dose of Skysona for intravenous infusion contains a minimum of 5.0 × 10^6 CD34+ cells/kg of body weight, suspended in a solution containing 5% dimethyl sulfoxide (DMSO).

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

12/11/2024	Added requirement of Molina Medical Director review.
10/09/2024	Modified exclusion criteria to include relevant requirements in the policy criteria. Overview, Summary of Evidence and References updated.
10/12/2023	No changes to policy criteria. Formatting changes and clarifications.
10/12/2022	New policy. IRO Peer Review 8/26/2022. Policy was reviewed by practicing physician Board-certified in Neurology with Special Qualifications in Child Neurology.

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