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

Last Approval: 10/12/2022
Next Review Due By: October 2023

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

Adrenoleukodystrophy (ALD) is a rare, inherited metabolic storage disease caused by a mutation in the ABCD1 gene that affects production of ALD protein (ALDP), resulting in the buildup of toxic very long-chain fatty acids (VLCFA) in the brain and spinal cord. Due to the accumulation of VLCFA in the adrenal cortex and white matter of the brain and spinal cord, myelin, the protective covering of the nerve cells in the brain responsible for thinking and motor control, gradually deteriorates. These nerves are incapable of transferring information to or from the brain in the absence of myelin. As ALD is an X-linked condition, the disease is significantly more severe in males, while most affected females exhibit spinal cord involvement-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 with approximately 35% to 40% males developing 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 and predominantly affects boys as an X-linked genetic disease. It is characterized by inflammatory demyelination leading to progressive loss of neurologic function and death. Mutations in the ABCD1 gene affect the production of ALDP and subsequently leads to accumulation of VLCFAs, primarily in the white matter of the brain and spinal cord. This accumulation leads to the breakdown of myelin, the protective sheath that nerve cells need to function effectively, especially for thinking and muscle control. The onset of symptoms of CALD typically occurs in childhood and most commonly presents in males between the ages of 4 and 10 years old (median age 7), with 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 available treatment varies depending on the clinical stage of the disease, and 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, consequently, of effective treatment for ALD. In the United States, newborn screening for ALD was added to the Recommended Universal Screening Panel in February 2016 and is now available in 19 states and the District of Columbia, accounting for more than 60% of newborns (HRSA, 2022). Plasma VLCFA levels and an ABCD1 gene mutation analysis molecular genetic test 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, if performed at the early stage of cerebral involvement, prior to the 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. Eli-cel is a one-time gene treatment intended to stabilize neurologic function and address the underlying cause of this irreversible neurodegenerative disease. According to the manufacturer, bluebird bio, eli-cel provides an alternative to allo-HSCT for 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 ex vivo transduction and the Lenti-D lentiviral vector. 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 the use of HSCs from a donor. Although 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 hours washout between conditioning and eli-cel infusion. FDA approval included a boxed warning for hematologic malignancy, including life-threatening cases of myelodysplastic syndrome, which has developed in patients treated with eli-cel in clinical studies. Additional considerations for prescribing clinicians are available from FDA (2022).

Eli-cel 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. **This 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 a confirmatory trial(s).**

The Biologics License Application (BLA) for eli-cel is supported by efficacy and safety data from the Phase 2/3 STARBEAM study (ALD-102) (N=32). The BLA also contains data for 23 subjects dosed in the Phase 3 ALD-104 study which has completed enrollment with **ongoing follow-up.** All patients who completed ALD-102, as well as those who will complete ALD-104, are invited to participate in a long-term follow-up study (LTF-304).

COVERAGE POLICY

Skysona (eli- cel) for the treatment of CALD **may be considered medically necessary** when **ALL** of 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; **AND**

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

AND

3. Clinical documentation and recent relevant evaluation, labs, and workup from member's medical records establishing eligibility for requested eli-cel gene therapy:
   a. Member has not received, or is being considered for other gene therapy, or investigational cellular therapy; **AND**

   b. No prior allogeneic transplant; **AND**

   c. Member is clinically stable and eligible for an allogeneic HSCT, but a human leukocyte antigen matched related HSC donor is not available; **AND**

   d. 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:

      - Hematological compromise as indicated by:
        - Peripheral blood absolute neutrophil count < 1500 cells/mm^3, or
        - Platelet count < 100,000 cells/mm^3, or

- Hemoglobin < 10 g/dL.

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

- Renal compromise as evidenced by abnormal renal function (actual or calculated creatinine clearance < 50 mL/min).

- Cardiac compromise as evidenced by left ventricular ejection fraction < 40%.

AND

e. A negative serology test for HIV, hepatitis B or C virus, or human T lymphotropic virus 1 (HTLV-1); **AND**

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; **AND**

h. For females of childbearing potential: Member is not pregnant or breast-feeding: 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.

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

There are no contraindications listed in the manufacturer's labeling at this time. The following are considered **exclusions** based on insufficient evidence:

1. Prior receipt of an allogeneic transplant or gene therapy
2. Any condition(s) that render MRI studies unfeasible (e.g., allergies to anesthetics or contrast agents)
3. Pregnancy: Not recommended for women who are pregnant; pregnancy after eli-cel infusion should be discussed with the treating physician.
4. Positive for HIV, hepatitis B or C virus (HBV or HCV), or 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.
5. Uncorrected bleeding disorder
6. Cardiac compromise as evidenced by left ventricular ejection fraction < 40%
7. Hematological compromise as indicated by:
   - Peripheral blood ANC count < 1500 cells/mm^3, or
   - Platelet count < 100,000 cells/mm^3, or
   - Hemoglobin < 10 g/dL.
8. Hepatic comprise indicated by:
   - AST value > 2.5 × ULN, or
   - ALT value > 2.5 × ULN, or
   - Total bilirubin value >3.0 mg/dL, except if there is a diagnosis of Gilbert's Syndrome and the individual is otherwise stable

9. Any condition which renders MRI studies not possible to perform (e.g., allergies to anesthetics or contrast agents)
10. Known hypersensitivity to protamine sulfate
11. Any contraindications to ANY of the following:
    - Granulocyte colony-stimulating factor or plerixafor during the mobilization of hematopoietic stem cells
    - Busulfan or fludarabine, including known hypersensitivity to the active substances or to any of the excipients in their formulations.

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

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

AGE RESTRICTIONS: ≥ 4 years and ≤ 17 years at the time of infusion

DOSING CONSIDERATIONS: Cell suspension for IV infusion. For autologous use only.
- A single dose for infusion containing a suspension of CD34+ cells in 1-2 infusion bags
- Minimum recommended dose: 5 x 10^6 CD34+ cells/kg
- Dose calculated based on patient weight prior to first apheresis and is specific to lot; see lot information sheet provided with product. Administer after a washout period of at least 48 hours after completion of conditioning (refer to specific protocols).

MONITORING PARAMETERS: Member will be monitored according to FDA-approved labeling.

Screen for HBV, HCV, HIV 1 and 2 (HIV-1/HIV-2), and human T-lymphotropic virus 1 and 2 prior to collection of cells for manufacturing. Monitor neutrophil counts until engraftment has been achieved. Monitor platelet counts frequently until platelet engraftment and platelet recovery are achieved; perform CBC and other appropriate testing whenever clinical symptoms suggestive of bleeding arise. Due to risk of hematologic malignancy, consider baseline CBC with differential, hematopathology review of peripheral blood smear, testing of germline mutations associated with hematologic malignancy, and bone marrow biopsy (core and aspirate) with flow cytometry, conventional karyotyping, and age-appropriate next-generation sequencing with a molecular panel, including coverage for gene mutations expected in myeloid and lymphoid malignancies.

Black Box Warning: Hematologic malignancy, including life-threatening cases of myelodysplastic syndrome, has occurred in patients treated with eli-cel. Patients have been diagnosed between 14 months and 7.5 years after eli-cel administration, and the cancers appear to be the result of the eli-cel lentiviral vector, Lenti-D, integration in proto-oncogenes. Monitor patients closely for evidence of malignancy through complete blood counts (CBC) at least every 6 months and through assessments for evidence for clonal expansion or predominance at least twice in the first year and annually thereafter.

Monitor lifelong for hematologic malignancies with a CBC (with differential) at least twice per year for at least 15 years after eli-cel treatment; perform integration-site analysis at least twice per year in the first year and then annually. Consider bone marrow evaluations as clinically indicated. If a malignancy occurs, contact the manufacturer (1-833-999-6378) for instructions on sample collection for testing. Monitor for signs/symptoms of hypersensitivity, bleeding, and/or infection.

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

ADMINISTRATION:
1. Eli-cel is considered a provider-administered therapy 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

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or rendering a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DRUG INFORMATION

ROUTE OF ADMINISTRATION: Intravenous Infusion

DRUG CLASS: Cellular Immunotherapy, Autologous; Gene Therapy, Autologous

FDA-APPROVED USES: Cerebral Adrenoleukodystrophy (CALD)
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.

This 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 a confirmatory trial(s).

Limitations of Use

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

FDA approval: September 16, 2022
Designations: Orphan Drug status (2012), Rare Pediatric Disease designation (2017), Breakthrough Therapy designation (2018)

COMPENDIAL APPROVED OFF-LABELED USES: None

BOXED WARNING: Hematologic malignancy

- Hematologic malignancy, including life-threatening cases of myelodysplastic syndrome, has occurred
- Diagnosis was between 14 months and 7.5 years after eli-cel, and cancers appear to be the result of lentiviral vector, Lenti-D, integration in proto-oncogenes
- Closely monitor for evidence of malignancy through CBCs at least every 6 months and through assessments for evidence of clonal expansion or predominance at least twice in the first year and annually thereafter; consider bone marrow evaluations as clinically indicated.

SUMMARY OF MEDICAL EVIDENCE

The BLA for Skysona (eli-cel) was supported by efficacy and safety data from the completed 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 patients with early, active CALD. Enrollment is complete and all patients have been treated in both studies; **follow-up in ALD-104 is ongoing.** All patients who completed ALD-102 and ALD-104 are eligible to participate in a long-term follow-up study (LTF-304) to continue monitoring safety and efficacy outcomes in boys treated with Skysona through 15 years post-treatment.

The safety and efficacy of Skysona were evaluated in two 24-month open-label, single-arm studies in patients with early, active CALD, as defined by a Loes score between 0.5 and 9 (inclusive) and gadolinium enhancement on MRI, as well as a neurologic function score (NFS) of 1, indicating limited changes in neurologic function. The NFS, which has a maximum score of 25, was used to assess 15 domains of neurological function. A total NFS of 0 indicates that there is no neurologic dysfunction or disease. Patients treated were also monitored for the emergence of six MFDs associated with CALD progression including loss of communication, cortical blindness, requirement for tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement.

The patients enrolled and treated with Skysona (Study 1, N=32; Study 2, N=35) all had elevated VLCFA levels as well as confirmed ABCD1 gene mutations. Patients who complete Studies 1 and 2 are enrolled in a subsequent and ongoing long-term follow-up study. The efficacy of Skysona was compared to an untreated natural history control. In the retrospective natural history study (Study 3), data for the Natural History Population were collected from existing medical records for CALD patients. The Natural History Population had early, active disease at the time of diagnosis, but gadolinium status was defined as either having a gadolinium enhancement MRI during the study or having an unknown gadolinium enhancement status and clinical course that suggested active disease.

A post hoc enrichment analysis in symptomatic patients assessed MFD-free survival from onset of symptoms (NFS ≥ 1) in Skysona-treated patients (n = 11) and untreated patients (n = 7). Skysona-treated patients had an estimated 72% likelihood of MFD-free survival at 24 months from time of first NFS ≥ 1, compared with untreated patients, who had only an estimated 43% likelihood of MFD-free survival. All patients from both studies have been treated (ALD-102 and ALD-104), and a follow-up study that will monitor patients through 15 years post-treatment is underway.

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 graft-versus-host disease (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 2/3 Study

STARBEAM study (ALD-102) was an open-label, single-arm, 24-month study that included a total of 32 patients (n=32) 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 CALD was defined as: a 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. All patients lacked a sibling donor with a compatible human leukocyte antigen for allo-HSCT. 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, and 46.9% were White/Caucasian. 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. All patients that completed ALD-102 enrolled for long-term follow-up in the LTF-304 study. The median duration of follow-up was 38.59 (range: 13.4-82.7) months. (ClinicalTrials.gov Identifier: NCT01896102)

The primary efficacy endpoint for the STARBEAM Study is the absence of 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: loss of ability to communicate, cortical blindness, need for tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement. The secondary efficacy endpoint of the study is the progression of the cerebral disease. This is evaluated by gadolinium enhancement on brain MRI (which is an indicator of neuroinflammation) and by the Neurologic Function Score. The NFS is a scoring system that is used to evaluate the severity of clinical deficits by scoring 15 symptoms across multiple domains. The safety profile of Lenti-D was also evaluated (side-effects and genome integration analysis of the gene).

At 24 months, 90.6% (29/32) of ALD-102 patients, 29 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. All ALD-102 patients were enrolled in a long-term follow-up study. The average duration of follow-up is about four years (49 months; range 13.4-88.1).

Interim Results at Completion of 24-Months

Eichler et al. (2017) published the interim results in 17 patients who completed the 24-month follow-up period. 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.

- 15 (88%) 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.
- No GVHD in the 15 remaining patients.
- 14 of these 15 patients had a score on the NFS of 0 or 1, which indicates no or minimal clinical symptoms.
- 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-month 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.

These preliminary findings indicate that eli-cel gene therapy for the treatment of CALD is at least as effective as conventional allo-HSCT. The absence of GVHD indicates that the procedure may be safer.

Phase 3 Studies

ALD-104 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).

The proportion of patients alive and free of MFDs at Month 24 is the primary efficacy endpoint, and the proportion of patients with neutrophil engraftment after eli-cel infusion is the primary safety endpoint (ClinicalTrials.gov Identifier: NCT03852498).

No study results posted on ClinicalTrials.gov for this study. **Estimated Study Completion Date: February 2024.**

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 (September 29, 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 that reached 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.

SUPPLEMENTAL INFORMATION

None.

CODING & BILLING INFORMATION

CPT	Description
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)

HCPCS	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

10/12/2022 MCPC New policy. IRO Peer Review. 8/26/2022. Policy was reviewed by practicing physician Board-certified in Neurology with Special Qualifications in Child Neurology.

REFERENCES

Government Agencies

1. Centers for Medicare and Medicaid Services (CMS). Medicare coverage database (no National Coverage Determination identified – search: elivaldogene autotemcel, cerebral adrenoleukodystrophy). Available from CMS.
2. ClinicalTrials.gov.
   - ALD-102 (NCT01896102). A study of the efficacy and safety of hematopoietic stem cells transduced with Lenti-D Lentiviral vector for the treatment of Cerebral Adrenoleukodystrophy (CALD). Updated April 25, 2022. Accessed September 2022.
   - ALD-104 (NCT03852498). A clinical study to assess the efficacy and safety of gene therapy for the treatment of Cerebral Adrenoleukodystrophy (CALD). Updated April 4, 2022. Accessed September 2022.
   - LTF-304 (NCT02698579). Long-term follow-up of participants with Cerebral Adrenoleukodystrophy who were treated with Lenti-D drug product. Updated August 12, 2022. Accessed September 2022.
3. Health Resources and Services Administration (HRSA). Newborn screening: X-linked adrenoleukodystrophy. Available from HRSA. Updated March 2022.
4. United States Food and Drug Administration (FDA)
   - FDA news release. Accelerated BLA approval. Updated September 16, 2022. Available from FDA. Accessed Sept. 2022.
   - FDA halts Bluebird bio clinical trial after patient develops MDS. August 13, 2021. Available from FDA. Accessed Sept. 2022.

Prescribing Information and Drug Compendia

1. Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. Available from ClinicalKey. Published 2021. Accessed August 2022. Registration and login required.
2. Drug Facts and Comparisons. Facts and comparisons eAnswers [online]. Available from Wolters Kluwer Health, Inc. Accessed September 2022. Registration and login required.
3. Skysona (elivaldogene autotemcel) [prescribing information]. Somerville, MA: Bluebird Bio Inc; September 2022.

Peer Reviewed Publications

1. bluebird bio receives FDA accelerated approval for SKYSONA® Gene Therapy for early, Active Cerebral Adrenoleukodystrophy (CALD). News release. bluebird bio. September 16, 2022.
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APPENDIX

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*