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## Elivaldogene autotemcel

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### Disclaimer

*Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.*

### Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

### Legislative Mandates

**EXCEPTION:** For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated, and coverage is not required for non-formulary drugs.

## Coverage

The use of elivaldogene autotemcel (Skysona™) **is considered not medically necessary** for all indications including treatment of cerebral adrenoleukodystrophy.

## Policy Guidelines

None.

## Description

Cerebral adrenoleukodystrophy (CALD) is an X-linked genetic neurodegenerative disease that most severely affects individuals assigned male at birth. The genetic mutation leads to impaired or loss of adrenoleukodystrophy protein (ALDP) expression.

X-linked adrenoleukodystrophy is established in a male (assigned male at birth or AMAB) with suggestive clinical findings and elevated very long chain fatty acids (VLCFA), with the majority having inherited a pathogenic variant in the *ABCD1* gene. While female (assigned female at birth or AFAB) carriers can develop spastic paraparesis most often in adulthood, adrenal function is generally not impaired. CALD typically only affects AMAB in childhood and AFAB with CALD are very rare. Defective function of ALDP leads to the accumulation of very long-chain fatty acids (VLCFAs), which occurs in plasma and all tissue types but most prominently in the adrenal cortex and white matter of the brain and spinal cord. VLCFAs initiate an inflammatory cascade ultimately leading to inflammatory cerebral demyelination. In general, once clinical symptoms appear, the clinical course is rapid with progressive cognitive and neurologic deficits leading to major disability including cortical blindness, incontinence, requirement for tube feeding, loss of communication, loss of ambulation, loss of voluntary movement, and ultimately premature death. Prior to the approval of elivaldogene autotemcel, there were no approved treatments for CALD in the United States (U.S.). Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered the standard of care and has been shown to stabilize neurologic function, with better outcomes observed in patients treated at the early stages of cerebral involvement and among those who receive human leukocyte antigen (HLA)-matched transplant versus HLA-mismatched transplant. Challenges associated with HSCT include serious immunologic complications, including transplant-related mortality, graft rejection, and graft-versus-host disease. Elivaldogene autotemcel is an autologous hematopoietic stem cell (HSC)-based gene therapy which adds functional copies of the *ABCD1*

cDNA into patients' HSCs through transduction of autologous CD34+ cells with Lenti-D lentiviral vector. After infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate into various cell types, including monocytes (CD14+) capable of producing functional ALDP. Functional ALDP can then participate in the local degradation of VLCFAs, which is believed to slow or possibly prevent further inflammation and demyelination.

## **Background**

### **Cerebral Adrenoleukodystrophy**

Adrenoleukodystrophy (ALD) is a rare neurodegenerative metabolic disorder caused by X-linked mutations in ABCD1 gene that lead to impaired peroxisomal expression of adrenoleukodystrophy protein (ALDP) which is needed to transport very long chain fatty acids (VLCFAs) into the peroxisome for degradation. (1) Impaired expression of ALDP leads to accumulation of VLCFAs, which occurs in plasma and all tissue types but most prominently in the adrenal cortex and white matter of the brain and spinal cord. Cerebral ALD (CALD) is the most severe form of ALD, often emerging in early childhood and characterized by rapidly progressive cerebral demyelination due to inflammatory cascade initiated by VLCFAs leading to irreversible loss of neurologic function and death. (1, 2) Approximately 40% of patients with ALD develop CALD. The diagnosis is made once there is evidence of cerebral demyelination on brain magnetic resonance imaging (MRI). Lesions are graded according to a Loes score, which assigns a severity score (0 to 34) based on location and extent of demyelination, as well as presence/absence of focal and/or global atrophy. A score of 0 indicates normal MRI (i.e., no cerebral disease), and higher scores indicate increased severity of cerebral lesions. (3) Because it is an X-linked recessive condition, it most severely affects those assigned male at birth (AMAB). While female (assigned female at birth or AFAB) carriers can develop spastic paraparesis most often in adulthood, adrenal function is generally not impaired. AFAB with CALD are very rare.

In general, the clinical course in childhood is rapid with progressive cognitive and neurologic deficits leading to major disability including cortical blindness, incontinence, requirement for tube feeding, loss of communication, loss of ambulation, and loss of voluntary movement and ultimately premature death. However, there is heterogeneity in the disease course marked by variable rates of progression depending on location, extent of contrast enhancement of lesions on brain MRI, age at presentation, and extent of neurologic and neurocognitive symptoms. (2, 4-10) See Table 1 for patterns of cerebral disease on MRI with prognostic implications. AMABs with CALD typically present with academic difficulties, inattention, or hyperactivity between 4 and 10 years of age. (4-6) Left untreated, the disease progresses to neurologic dysfunction, disability, and ultimately death, usually by the second decade of life from disease complications. Approximately 30% to 50% of untreated AMABs with CALD die within 5 years of diagnosis, and nearly all survivors have severe neurologic dysfunction or disability. (4) The estimated U.S. prevalence is at most 800 AMABs based on estimates, from Mosser et al. 1993 and Moser et al. 2000. (4, 11)

In February 2016, adrenoleukodystrophy was added to the Recommended Uniform Screening Panel in the U.S. (12) With increasing identification of X-ALD cases due to newborn screening

and genetic testing of family members of affected individuals, routine MRI screening now allows for diagnosis of CALD at some of the earliest stages of cerebral disease, often prior to onset of neurologic dysfunction or neurocognitive changes. (6, 13-15) There is lack of data on an appropriate natural history (i.e., untreated) population that has been followed from such an early stage of disease to understand the clinical course of asymptomatic early, active cerebral disease if left untreated.

**Table 1. Patterns of Cerebral Disease with Prognostic Implications (7)**

| <b>MRI Pattern</b>                                                | <b>Prognostic Implication</b>       | <b>Disease Progression</b>                                                                                                                 |
|-------------------------------------------------------------------|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Pattern 1: Parieto-occipital white matter                         | Typically presenting in childhood   | Patients experience rapid disease progression if the pattern is present at an early age, particularly if gadolinium enhancement is present |
| Pattern 2: Frontal white matter                                   | Typically presenting in adolescence | Patients experience rapid disease progression if the pattern is present at an early age, particularly if gadolinium enhancement is present |
| Pattern 3: Isolated pyramidal tract                               | Typically presenting in adulthood   | Disease progression is generally slower                                                                                                    |
| Pattern 4: Cerebellar white matter                                | Typically presenting in adolescence | Disease progression is generally slower                                                                                                    |
| Pattern 5: Concomitant parieto-occipital and frontal white matter | Typically presenting in childhood   | Uncommon and is associated with much more rapid progression than other patterns                                                            |
| Other: Any pattern other than those characterized by patterns 1-5 | Not known                           | Not known                                                                                                                                  |

MRI: magnetic resonance imaging.

### *Current Standard of Care*

Until 2022 there were no Food and Drug Administration (FDA)-approved treatments for CALD in the United States. Allo-hematopoietic stem cell transplantation (HSCT) has been the standard of care since approximately 2001 (2) and is the only therapy considered by experts to be disease-modifying (i.e., able to slow or stabilize disease progression). (9, 16-18) Retrospective studies have shown that outcomes with allo-HSCT are most favorable when performed at the early stages of cerebral involvement prior to onset of significant neurologic dysfunction or radiographic disease burden and with a graft from a matched sibling donor. (16, 19) Additionally, studies have demonstrated that radiographic and clinical disease progression may occur in the initial 12 to 24 months following treatment with allo-HSCT before disease stabilization is achieved. (2, 3, 9, 10, 16) As such, allo-HSCT is performed in the early, active radiographic course of disease (Loes score 0.5-9 with gadolinium enhancement on brain MRI), which often corresponds to a time when patients are asymptomatic or mildly symptomatic (neurologic function score [NFS] 0 or 1). The goal of treatment in this early, active phase of

disease is to treat prior to the onset of significant neurologic dysfunction in an effort to prevent progression to disability and death, which is often rapid and more difficult to stabilize once disease is symptomatic. It has also been observed that allo-HSCT may increase rapidity of disease progression in patients with advanced cerebral disease (Loes score >9) and therefore is no longer recommended for patients who meet this criterion. (9, 10, 16) While studies have demonstrated efficacy of allo-HSCT as compared to the natural history of disease among individuals with early symptomatic disease, long-term efficacy of allo-HSCT as compared to the natural history of disease in the earliest asymptomatic disease stages with minimal radiographic cerebral disease burden is unknown because of lack of data on natural disease progression of asymptomatic, early, active cerebral disease. (20) Allo-HSCT is associated with known risks, including graft rejection, graft versus host disease, and infection, and these risks are higher with alternative (human leukocyte antigen [HLA]- mismatched or non-sibling HLA-matched) donors. HLA-matched sibling donors are only available for ≤30% of patients. (16) Morbidity and mortality following allo-HSCT are significant, with 5-year survival varying between 50% and 95%, depending on donor type, conditioning regimens, and stage of disease at time of treatment, with percentages reflecting death from disease progression and transplant-related causes. (9, 10)

### **Regulatory Status**

On September 19, 2022, Skysona™ (elivaldogene autotemcel) was approved by the FDA to slow the progression of neurologic dysfunction in boys 4 to 17 years of age with early, active cerebral adrenoleukodystrophy (CALD). Early, active CALD refers to asymptomatic or mildly symptomatic (NFS ≤1) boys who have gadolinium enhancement on brain MRI and Loes scores of 0.5 to 9. In 2025, the indication for Skysona was revised to state that Skysona should only be given to CALD patients without an available HLA-matched donor for allogeneic hematopoietic stem cell transplant. The change was prompted by new safety information about the increased risk of hematologic malignancy with Skysona.

Skysona's indication is approved under accelerated approval based on 24-month major functional disability-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

The FDA has requested Bluebird Bio to conduct 2 post-marketing studies to verify the clinical benefit.

## **Rationale**

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or

worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

### **Cerebral Adrenoleukodystrophy**

#### **Clinical Context and Therapy Purpose**

The purpose of elivaldogene autotemcel in individuals who have early, active cerebral adrenoleukodystrophy (CALD) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

#### ***Populations***

The relevant population of interest is individuals 4 to 17 years of age with early, active CALD. Early, active CALD refers to asymptomatic or mildly symptomatic (neurologic function score [NFS]  $\leq 1$ ), generally seen in individuals assigned males at birth (AMAB), who have gadolinium enhancement on brain magnetic resonance imaging (MRI) and Loes scores of 0.5 to 9.

#### ***Interventions***

The therapy being considered is elivaldogene autotemcel. In this gene therapy protocol, hematopoietic stem cells are mobilized using granulocyte colony-stimulating factor (G-CSF) and plerixafor followed by apheresis to obtain a CD34+ cell-enriched population. These cells are then transduced *ex vivo* by lentiviral vector carrying *ABCD1* cDNA that encodes normal adrenoleukodystrophy protein (ALDP). Individuals receive myeloablative conditioning with busulfan to deplete endogenous hematopoietic stem cells and lymphodepletion with cyclophosphamide, enabling therapeutic repopulation of the individual bone marrow with hematopoietic stem cells containing the transgene. Treatment with elivaldogene autotemcel requires inpatient hospitalization.

#### ***Comparators***

The following strategies are currently being used to treat early, active CALD: allogenic hematopoietic stem cell transplant (allo-HSCT).

## Outcomes

The general outcomes of interest are overall survival, disease-specific survival, change in disease status, functional outcomes, quality of life, treatment-related morbidity and treatment-related mortality (Table 2). Follow-up at 15 years is of interest to monitor outcomes.

**Table 2. Health Outcome Measures Relevant to Cerebral Adrenoleukodystrophy**

| Outcome                               | NFS Score                                                                                                                                                                                                                                                                                                                                                                                                    | MFD                                                                                                                                                                                                                         | Loes score                                                                                                                                                                                                                                                                                                                             |
|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Measure (Units)</b>                | The NFS, a 25-point composite scale that assesses both minor and major functional disabilities. It focuses on 15 domains of neurologic function, is traditionally used to evaluate the clinical status of CALD patients. A score of 0 indicates absence of clinical signs of cerebral disease (i.e., asymptomatic), and higher scores correspond to increasing severity of neurological dysfunction. (4, 16) | The MFDs are a subset of the NFS.                                                                                                                                                                                           | Lesions are graded according to a Loes score, which assigns a severity score (0-34) based on location and extent of demyelination, as well as presence/absence of focal and/or global atrophy. A score of 0 indicates a normal MRI (i.e., no cerebral disease), and higher scores indicate increased severity of cerebral lesions. (3) |
| <b>Description and Administration</b> | <p>Calculated as a total score of the following components:</p> <ul style="list-style-type: none"> <li>Hearing/auditory processing problems (1)</li> <li>Aphasia/apraxia (1)</li> <li>Loss of communication (3)</li> <li>Vision impairment (1)</li> <li>Cortical blindness (2)</li> </ul>                                                                                                                    | <p>The 6 MFDs are:</p> <ul style="list-style-type: none"> <li>Loss of communication</li> <li>Cortical blindness</li> <li>Requirement for tube feeding</li> <li>Total incontinence</li> <li>Wheelchair dependence</li> </ul> | <p>Scores are based on the location and features of MRI lesions in the brain:</p> <ul style="list-style-type: none"> <li>Parieto-occipital white matter (up to 4)</li> <li>Anterior temporal white matter (up to 4)</li> </ul>                                                                                                         |



|                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                           |
|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                          | <ul style="list-style-type: none"> <li>Swallowing dysfunctions (2)</li> <li>Tube feeding (2)</li> <li>Running difficulties (1)</li> <li>Walking difficulties/spasticity (1)</li> <li>Spastic gait (need assistance) (2)</li> <li>Wheelchair dependence (2)</li> <li>No voluntary movement (3)</li> <li>Episodes of incontinence (1)</li> <li>Total incontinence (2)</li> <li>Nonfebrile seizures (1)</li> <li>Possible total score=25</li> </ul> | <ul style="list-style-type: none"> <li>Complete loss of voluntary movement</li> </ul>                                               | <ul style="list-style-type: none"> <li>Frontal white matter (up to 4)</li> <li>Corpus callosum (up to 5)</li> <li>Visual pathway (up to 4)</li> <li>Auditory pathway (up to 4)</li> <li>Projection fibers (up to 2)</li> <li>Cerebellum (up to 2)</li> <li>Basal ganglia (up to 1)</li> <li>Atrophy (up to 4)</li> <li>Possible total score=34</li> </ul> |
| <b>Thresholds for Improvement/Decline or Clinically Meaningful Difference (if known)</b> | The NFS is widely accepted, and interobserver reliability of >95% has been reported. (4, 16)                                                                                                                                                                                                                                                                                                                                                     | The MFDs as were chosen by a group of CALD experts based on their clinical significance and impact on independent functioning. (20) | The maximum severity score is 34; any score $\geq 0.5$ is considered abnormal. (7) Early CALD has been described as patients with Loes scores >0 to 9 in the literature. (9, 21, 22)                                                                                                                                                                      |

CALD: cerebral adrenoleukodystrophy; MFD: major functional disabilities; MRI: magnetic resonance imaging; NFS: Neurologic Function Score.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.



- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

The clinical development program is summarized in Table 3 and consists of 2 pivotal interventional studies (ALD-102 and ALD-104). In addition, 2 non-interventional clinical studies (ALD-101 and ALD-103) provided background and comparative information about the natural history of untreated CALD and outcomes of allo-HSCT. The pivotal interventional studies are single-arm, open-label trials. The severity of CALD, the rarity of the disease, the lack of authorized treatment options, the inability of transplant to be blinded, and the risk of disease progression during the time required to conduct a donor match for an allo-HSCT comparator arm precluded the conduct of a RCT in the target patient population.

The original indication proposed by Bluebird in its biologics license application (BLA) included only those individuals with early CALD who did not have an available and willing human leukocyte antigen (HLA)-matched sibling hematopoietic stem cell (HSC) donor. (20) The original BLA included efficacy data from 32 participants from study ALD-102 for the primary analysis, as well 14 additional participants from study ALD-104 in a pooled secondary analysis. These data from single-arm, prospective, interventional studies were compared with nonconcurrent historical controls from studies ALD-101 and ALD-103.

The Food and Drug Administration (FDA) review team considered the potential for traditional approval for this limited population (early CALD who did not have an available and willing HLA-matched sibling HSC donor) but found multiple limitations in the analyses submitted by the sponsor. These included a lack of comparability between the elivaldogene autotemcel-treated participants and historical controls that were used to determine the clinical benchmark to define the primary endpoint of the pivotal trial. Untreated individuals in the historical control arm were diagnosed at a time when disease understanding was evolving, contrast was not routinely used for MRI assessments, and delayed diagnosis was common. The length of the study (24 months) was insufficient to ensure that the results demonstrating superiority of elivaldogene autotemcel or allo-HSCT over no treatment in the pivotal analysis were not simply an artifact of lead-time bias. FDA reviewers were also skeptical of the imputation strategy that over-estimated the number of failure events (and thus dropped the lower bound of the 95% CI) in the allo-HSCT-treated early, active disease subpopulation from ALD-101.

Given these limitations and lack of adequate data to support durability, the FDA review team instead recommended an accelerated approval based on an exploratory post-hoc subset analysis of enriched sample that comprised of 11 treated individuals compared with 7 untreated individuals who had symptomatic disease at some time during the study (either NFS=1 at baseline or development of symptoms [i.e., NFS ≥1] during the course of follow-up). Selection of study participants was restricted to those with symptomatic disease because exploratory analysis by FDA reviewers (data not disclosed) showed a rapid disease progression after documentation of first NFS ≥1, typically peaking to maximum documented NFS within 24

months among untreated individuals. Data reported in the prescribing label are included in the current review. (23)

While the 2021 accelerated approval initially removed the restriction to donor-ineligible patients, the indication was revised in August 2025 in response to new safety findings of increased risk of hematologic malignancy. As of August 7, 2025, Skysona is approved for boys with early, active CALD who do not have an available HLA-matched donor for allogeneic hematopoietic stem cell transplant. (23)

**Table 3. Clinical Development Program for Elivaldogene Autotemcel (20)**

| Study   | NCT No         | Status                                                                               | Study Dates            | Objective                                                                                                  | Sample Size                                      | Median Follow-Up (min, max)                                   |
|---------|----------------|--------------------------------------------------------------------------------------|------------------------|------------------------------------------------------------------------------------------------------------|--------------------------------------------------|---------------------------------------------------------------|
| ALD-101 | Not registered | Complete                                                                             | Apr 2011 to May 2012   | Evaluate the natural history of disease in untreated CALD<br>Evaluate efficacy/safety of allo-HSCT in CALD | 137 (65 treated with allo-HSCT and 72 untreated) | 39.2 (0.4, 11.5) months                                       |
| ALD-103 | NCT02204904    | Complete (24)                                                                        | April 2015 to Dec 2019 | Evaluate efficacy/safety for 4 years following allo-HSCT in CALD                                           | 59 treated with allo-HSCT                        | 23.0 (0.9, 49.5) months                                       |
| ALD-102 | NCT01896102    | Complete (25) (October 2013 and July 2015)<br>(26) (October 2013 through April 2019) | Aug 2013 to April 2019 | Evaluate efficacy/safety for 2 years following eli-cel treatment in CALD                                   | 32 treated with eli-cel                          | 6 years                                                       |
| ALD-104 | NCT03852498    | Completed with results posted (27)                                                   | Jan 2019 to July 2023  | Evaluate efficacy/safety for 2 years following eli-cel treatment in CALD                                   | 35 treated with eli-cel                          | 24 months; participants' follow-up remains ongoing in LTF-304 |
| LTF-304 | NCT02698579    | Ongoing                                                                              | Jan 2016 to ongoing    | Evaluate efficacy/safety for 15 years following eli-cel treatment in CALD                                  | 28 treated with eli-cel                          |                                                               |

allo-HSCT: allogeneic hematopoietic stem cell transplant; CALD: cerebral adrenoleukodystrophy; eli-cel: elivaldogene autotemcel; NCT: national clinical trial, No: number.

## Nonrandomized Studies

### *Efficacy*

Study characteristics, baseline demographics characteristics, and results are summarized in Tables 4 through 6, respectively.

Eichler et al. (2024) published the results of ALD-102 at a median follow-up of 6 years. (26) This study evaluated elivaldogene autotemcel in boys aged  $\leq 17$  years with early CALD who did not have an available and willing HLA-matched sibling HSC donor. A total of 32 participants received elivaldogene autotemcel. The primary efficacy endpoint was survival without any of 6 major functional disabilities (MFDs) at month 24. Secondary endpoints included overall survival and change in NFS. A description of the 6 MFDs and the NFS is outlined in Table 2. At baseline, median age was 6 years (range, 3 to 13 years), median Loes score was 2 (range, 1 to 9), and NFS was 0 or 1. At month 24, 29 of 32 patients (91%; 95% CI, 75 to 98) were alive and free of MFDs. Regarding secondary endpoints at 24 months, the overall survival was 94% (30 of 32 patients) and the NFS was stable in 29 of 30 evaluable patients (97%; 95% CI, 83 to 100). At month 48, survival free of MFDs was 91% and the overall survival was 94%. At the most recent follow-up (median, 60.6 months), 26 patients (81%) remained free of MFDs. NFS remained stable in 30 of 32 patients (94%), with 88% maintaining scores of 0 or 1. Serious adverse events occurred in 22 of 32 participants, primarily during conditioning. At month 24 of the study, a total of 3 patients had adverse events attributed to elivaldogene autotemcel. From month 24 through the most recent assessment, 10 of the 29 patients remaining in the study had at least 1 adverse event and 7 of these patients had at least 1 serious adverse event. One participant developed myelodysplastic syndrome (MDS) at month 92, attributed to vector insertion. This participant underwent successful allogeneic transplantation at month 95 with no indication of MDS recurrence at month 120.

The results of NCT03852498 (ALD-104) were posted to Clinicaltrials.gov in May 2024. (27) This study evaluated elivaldogene autotemcel in boys aged  $\leq 17$  years with early CALD, but did not stipulate that participants could not have a willing HLA-matched sibling HSC donor to be eligible for participation. A total of 35 participants received elivaldogene autotemcel. The primary efficacy endpoint, survival without any MFDs at month 24, was achieved in 85.7% (95% CI, 69.7 to 95.2%) of participants. All 35 participants were alive at month 24. A change in NFS  $\leq 3$  occurred in 4 (11.4%) participants, and a change  $>3$  occurred in 2 (5.7%) participants.

The exploratory major functional disability (MFD)-free survival analysis, summarized in the Skysona prescribing label, compared subsets of the early active disease natural history subpopulation (n=7) and elivaldogene autotemcel treated subpopulation (n=11). (23) In this analysis, time zero was the date of the first NFS  $\geq 1$ . Although these subpopulations were “homogenized” by selecting participants with similar prognostic features, imbalance in known prognostic variables persisted at baseline. For example, the natural history subpopulation was older, with a median age at first NFS  $\geq 1$  higher than the treated subpopulation. The median Loes score was also higher (5 vs. 2.5) in the natural history subpopulation versus the treated subpopulation. The distribution of brain MRI patterns of disease also varied across

subpopulations. Isolated pyramidal tract disease is reported to be generally associated with slower progression of disease. Two out of 72 (2.7%) participants in the ALD-101 study (untreated group) and 10 out of 67 (14.9%) participants in the ALD-102 and -104 (elivaldogene autotemcel treated) had isolated pyramidal tract disease on brain MRI. The estimated MFD-free survival at month 24 from time of first NFS  $\geq 1$  were 72% (95% CI, 35% to 90%) for the symptomatic elivaldogene autotemcel-treated subpopulation and 43% (95% CI, 10% to 73%) for the natural history subpopulations. In another exploratory analysis reported in the prescribing label, 7 of 36 (19%) evaluable elivaldogene autotemcel-treated patients had a cerebral MRI Loes score increase of  $\geq 6$  points while 3 of 30 (10%) evaluable allo-HSCT patients had a cerebral MRI Loes score increase of  $\geq 6$  points. Clinical implications of a higher Loes score among elivaldogene autotemcel-treated participants relative to allo-HSCT treated participants is unclear. It is noteworthy that the reported primary evidence of efficacy lies in the outcomes of subjects with parieto-occipital disease, as the pattern was the most common across studies, presents the earliest (in childhood), and is 1 of the most rapidly progressive if left untreated.

### *Safety*

Elivaldogene autotemcel was approved with a Boxed Warning due to hematologic malignancy, including life-threatening cases of myelodysplastic syndrome (MDS) and acute myeloid leukemia in patients between 14 months and 10 years after treatment with the gene therapy. (23) As of July 2025, hematologic malignancies have been diagnosed in 10/67 (15%) clinical study patients. At diagnosis, all patients had high-frequency integrations in oncogenes; most of which were in *MECOM*. Pathological diagnoses ranged between MDS-unilineage dysplasia to acute myeloid leukemia. As of July 2025, 9 of the 10 patients had received allogeneic hematopoietic stem cell transplant. One of the patients with MDS relapsed 6 months after an allogeneic transplant and required re-treatment of MDS.

Early diagnosis of hematologic malignancy can be critically important; therefore, as per the prescribing label, for at least the first 15 years after treatment with elivaldogene autotemcel, patients should be monitored via complete blood count (with differential) at least every 3 months and via integration site analysis or other testing for evidence of clonal expansion and predominance at least twice in the first year and then annually. In addition, appropriate expert consultation and additional testing such as more frequent complete blood count (with differential) and integration site analysis, bone marrow studies, and gene expression studies in the following settings after treatment with elivaldogene autotemcel:

- Delayed or failed engraftment of platelets or other cell lines (while all patients are at risk for hematologic malignancy, patients who do not achieve unsupported platelet counts of  $\geq 20 \times 10^9/L$  on or after day 60 appear to be at higher risk); or
- New or prolonged cytopenias; or
- Presence of clonal expansion or predominance (e.g., increasing relative frequency of an integration site, especially if  $\geq 10\%$  and present in *MECOM* or another proto-oncogene known to be involved in hematologic malignancy).

An exploratory analysis for overall survival due to concerns about treatment-related toxicities reported in the prescribing label demonstrates a survival advantage of elivaldogene autotemcel

as compared to allo-HSCT from an HLA-mismatched donor, with early mortality in the HLA-mismatched allo-HSCT subpopulation largely attributed to allo-HSCT-related toxicities. Overall survival was analyzed as time-to-event Kaplan-Meier estimates comparing elivaldogene autotemcel (entire efficacy population, N=61) to early, active allo-HSCT subpopulations by donor type: HLA-matched allo-HSCT subpopulation (n=34) and HLA-mismatched allo-HSCT subpopulation (n=17) at 24 months. (23)

Another potential risk of elivaldogene autotemcel, which occurred in 1 patient, was failure of the transduced cells to persist. Six months after treatment, the individual had percent ALDP + cells below the limit of quantitation, gadolinium enhancement on MRI, and an increase in Loes score. The individual also experienced a steep decline in peripheral blood vector copy number below the limit of quantitation within 9 months after treatment with elivaldogene autotemcel. Subsequent MRIs provided evidence of further progression of CALD, and the individual therefore underwent allo-HSCT. Notably, this participant had a full deletion of the *ABCD1* gene, and an immune response is thought to have caused the failure of vector-containing cells to persist. Thus, an immune response to elivaldogene autotemcel may limit the persistence of descendent cells of gene therapy, causing rapid loss of efficacy in patients with full deletions of the *ABCD1* gene. (23)

**Table 4. Summary of Key Nonrandomized Trials**

| <b>Study</b>                          | <b>Eichler et al. (2024) (26); ALD-102</b>                                                                                                                                                                             | <b>NCT03852498 (27); ALD-104</b>                                                                                                                                                                                                                               | <b>Skysona prescribing label (2025) (23)</b>                                                                                                                                                                                                                                                           |
|---------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Elivaldogene Autotemcel</b>        | Phase 2-3, single-arm                                                                                                                                                                                                  | Phase 3, single-arm                                                                                                                                                                                                                                            | Post-hoc analysis                                                                                                                                                                                                                                                                                      |
| <b>Historical Control (Untreated)</b> | NA                                                                                                                                                                                                                     | NA                                                                                                                                                                                                                                                             | Argentina, Australia, France, Germany, United Kingdom and United States (8 sites, 3 in US)                                                                                                                                                                                                             |
| <b>Dates</b>                          | October 2013 through April 2019                                                                                                                                                                                        | Jan 2019 through July 2023                                                                                                                                                                                                                                     | 2000-2008                                                                                                                                                                                                                                                                                              |
| <b>Participants (Treated Group)</b>   | <b>Inclusion</b> <ul style="list-style-type: none"> <li>• Males ≤17 years of age with early-stage CALD confirmed by biochemical and genetic testing</li> <li>• GdE+ demyelinating lesions</li> <li>• NFS ≤1</li> </ul> | <b>Inclusion</b> <ul style="list-style-type: none"> <li>• Males ≤17 years of age with early-stage CALD confirmed by biochemical and genetic testing</li> <li>• GdE+ demyelinating lesions</li> <li>• NFS ≤1</li> <li>• Loes score between 0.5 and 9</li> </ul> | <b>Inclusion</b> <ul style="list-style-type: none"> <li>• Assigned male at birth and ≤17 years of age</li> <li>• Active CALD as defined by elevated VLCFA levels, and brain MRI demonstrating Loes score between 0.5 and 9 (inclusive) on the 34-point scale and GdE+ demyelinating lesions</li> </ul> |

|                           |                                                                                                                                                                                                       |                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                           | <ul style="list-style-type: none"> <li>Loes score between 0.5 and 9</li> </ul> <p>Exclusion</p> <ul style="list-style-type: none"> <li>Having a willing HLA-matched sibling donor for HSCT</li> </ul> | <p>Exclusion</p> <ul style="list-style-type: none"> <li>Received allo-HSCT or previous gene therapy</li> </ul> | <ul style="list-style-type: none"> <li>Symptomatic disease at some time during the study (either NFS=1 at baseline or development of symptoms (NFS <math>\geq</math>1) during the course of follow-up)</li> <li>Followed for at least 24 months after onset of symptomatic disease (NFS <math>\geq</math>1) or had an MFD or death</li> </ul> <p>Exclusion</p> <ul style="list-style-type: none"> <li>Received allo-HSCT or previous gene therapy</li> <li>Having a willing 10/10 HLA-matched sibling donor (excluding female heterozygotes)</li> </ul> |
| <b>Historical Control</b> | NA                                                                                                                                                                                                    | NA                                                                                                             | <ul style="list-style-type: none"> <li>Same as treated group except may have a brain MRI with GdE+ at any time during follow-up in the study OR unknown gadolinium status (due to lack of routine use at the time many natural history subjects were diagnosed) with clinical course suggestive of active disease</li> </ul>                                                                                                                                                                                                                            |
| <b>Follow-up</b>          | Median, 6 years                                                                                                                                                                                       | 24 months; ongoing in LTF-304 (NCT02698579)                                                                    | 24 months                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

allo-HSCT: allogenic hematopoietic stem cell transplant; CALD: cerebral adrenoleukodystrophy; GdE+: gadolinium enhancement on MRI; HLA: human leukocyte antigen; HSCT: hematopoietic stem cell transplant; MFD: major functional disability; MRI: magnetic resonance imaging; N/A: not applicable; NFS: Neurologic Functional Score; VLCFA: very long chain fatty acids.

**Table 5. Summary of Baseline Demographics and Disease Characteristics in Key Studies (23, 26)**

| Patient Characteristics                                                 | Elivaldogene Autotemcel | Historical Control (Untreated) |
|-------------------------------------------------------------------------|-------------------------|--------------------------------|
| <b>Eichler et al. (2024) (26); ALD102</b>                               |                         |                                |
| n                                                                       | 32                      | N/A                            |
| Median age (range), years                                               | 6 (3, 13)               |                                |
| Median duration of follow-up (range), months                            | 60.2 (13.4, 106.9)      |                                |
| Median baseline Loes score (range)                                      | 2 (1, 9)                |                                |
| Median neurologic function score (range)                                | 0 (0, 1)                |                                |
| Median time from enrollment to elivaldogene autotemcel infusion (range) | 67 (58, 89)             |                                |
| <b>NCT03852498 (27); ALD-104</b>                                        |                         |                                |
| Mean age (SD), yrs                                                      | 7 (2.1)                 |                                |
| <b>Skysona prescribing label (2025) (23)</b>                            |                         |                                |
| n                                                                       | 11                      | 7                              |
| Median age at CALD diagnosis (range), yrs                               | 6 (1, 10)               | 9 (5, 15)                      |
| Median age at treatment (range), yrs                                    | 6 (4, 10)               | NA                             |
| Median age at first NFS $\geq 1$ (range), yrs                           | 7 (4, 10)               | 10 (5, 17)                     |
| Baseline brain MRI pattern of disease, n (%)                            |                         |                                |
| Parieto-occipital                                                       | 10 (91)                 | 4 (57)                         |
| Frontal                                                                 | 0                       | 2 (29)                         |
| Pyramidal tract                                                         | 1 (9)                   | 1 (14)                         |
| Baseline NFS, n (%)                                                     |                         |                                |
| 0                                                                       | 9 (82)                  | 6 (86)                         |
| 1                                                                       | 2 (18)                  | 1 (14)                         |
| At time of first NFS $\geq 1$ , n (%)                                   |                         |                                |
| NFS total score =1                                                      | 10 (91)                 | 6 (86)                         |
| NFS total score >1                                                      | 1 (9)                   | 1 (14)                         |
| Median baseline Loes score (range)                                      | 2.5 (1, 9)              | 5 (2, 9)                       |

<sup>a</sup> At time of first NFS  $\geq 1$ , 1 elivaldogene autotemcel study participant had a total score of 2, and 1 historical control study participant had a total score of 3.

CALD: cerebral adrenoleukodystrophy; MRI: magnetic resonance imaging; NA: not available; N/A: not applicable; NFS: Neurologic Function Score; SD: standard deviation.

**Table 6. Summary of Results**

| Outcome                                    | Elivaldogene Autotemcel             | Historical Control (Untreated) |
|--------------------------------------------|-------------------------------------|--------------------------------|
| <b>Eichler et al. (2024) (26); ALD-102</b> |                                     |                                |
| n                                          | 32                                  | N/A                            |
| <i>Efficacy</i>                            |                                     |                                |
| MFD-free survival                          | 24 months: 91% (95% CI, 75% to 98%) |                                |



|                                                                               |                                                                                                                                                                                                                                                                                                                                   |                          |
|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
|                                                                               | Median follow-up, 60.6 months: 81%                                                                                                                                                                                                                                                                                                |                          |
| Overall survival                                                              | Month 24, 94%<br>Month 48, 94%                                                                                                                                                                                                                                                                                                    |                          |
| Stable NFS                                                                    | Month 24: 97% (95% CI, 83% to 100%)<br><br>Median follow-up, 6 years: 94%                                                                                                                                                                                                                                                         |                          |
| NFS=0 or 1                                                                    | Median follow-up, 6 years: 88%                                                                                                                                                                                                                                                                                                    |                          |
| <b>Safety</b>                                                                 |                                                                                                                                                                                                                                                                                                                                   |                          |
| At least 1 adverse event attributed to elivaldogene autotemcel                | <ul style="list-style-type: none"> <li>• Mobilization to before conditioning, n=0</li> <li>• Conditioning to before neutrophil engraftment, n=2</li> <li>• Neutrophil engraftment through Month 12, n=1</li> <li>• After Month 12 through Month 24, n=0</li> <li>• After Month 24 through most recent assessment, n=1</li> </ul>  |                          |
| At least 1 serious adverse event                                              | <ul style="list-style-type: none"> <li>• Mobilization to before conditioning, n=1</li> <li>• Conditioning to before neutrophil engraftment, n=8</li> <li>• Neutrophil engraftment through Month 12, n=12</li> <li>• After Month 12 through Month 24, n=4</li> <li>• After Month 24 through most recent assessment, n=7</li> </ul> |                          |
| <b>NCT03852498 (27); ALD-104</b>                                              | 35                                                                                                                                                                                                                                                                                                                                | N/A                      |
| 24-month MFD-free survival                                                    | 85.7% (95% CI, 69.7% to 95.2%)                                                                                                                                                                                                                                                                                                    |                          |
| 24-month overall survival                                                     | 100%                                                                                                                                                                                                                                                                                                                              |                          |
| 24-month stable                                                               | 94.3%                                                                                                                                                                                                                                                                                                                             |                          |
| <b>Skysona prescribing label (2025) (23)</b>                                  |                                                                                                                                                                                                                                                                                                                                   |                          |
| n                                                                             | 11                                                                                                                                                                                                                                                                                                                                | 7                        |
| Efficacy                                                                      |                                                                                                                                                                                                                                                                                                                                   |                          |
| 24-month MFD-free survival <sup>a</sup>                                       | 72% (95% CI, 35% to 90%)                                                                                                                                                                                                                                                                                                          | 43% (95% CI, 10% to 73%) |
| Safety (Grade 3 or higher adverse reactions in >40% of patients) <sup>b</sup> |                                                                                                                                                                                                                                                                                                                                   |                          |
| n                                                                             | 67                                                                                                                                                                                                                                                                                                                                | NA                       |
| Febrile neutropenia <sup>c</sup>                                              | 49 (73%)                                                                                                                                                                                                                                                                                                                          | NA                       |

|                        |           |    |
|------------------------|-----------|----|
| Mucositis <sup>d</sup> | 34 (51%)  | NA |
| Decreased appetite     | 27 (40%)  | NA |
| Leukopenia             | 67 (100%) | NA |
| Lymphopenia            | 67 (100%) | NA |
| Thrombocytopenia       | 67 (100%) | NA |
| Neutropenia            | 64 (96%)  | NA |
| Anemia                 | 56 (84%)  | NA |
| Hypokalemia            | 28 (42%)  | NA |

CI: confidence interval; MFD: major functional disability; NA: not available; N/A: not applicable; NFS: Neurologic Function Score.

<sup>a</sup> Kaplan-Meier time-to-event analysis defined as estimated time to progression to MFD or death from first NFS  $\geq 1$ . The MFDs are defined as: loss of communication, cortical blindness, requirement for tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement.

<sup>b</sup> Includes adverse events associated with conditioning.

<sup>c</sup> Febrile neutropenia includes febrile bone marrow aplasia and febrile neutropenia.

<sup>d</sup> Mucositis includes anal inflammation, colitis, gastrointestinal inflammation, mucosal inflammation, proctitis, and stomatitis.

The purpose of the study limitations tables (see Tables 7 and 8) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence and provides the conclusions on the sufficiency of evidence supporting the position statement. There are critical statistical and methodological limitations to a post-hoc analysis using a historical control with a limited sample size to make inferential claims about efficacy. There were known differences in the baseline prognostic variables such as age at enrollment, age at first NFS  $\geq 1$ , Loes score, and distribution of brain MRI pattern of disease between the 2 groups. The data collected in the historical untreated cohort were from a time (1988 to 2010) when delayed diagnosis was more common due to decreased availability of genetic testing, lack of newborn screening, and HSCT not having yet been optimized. Study participants were, therefore, generally older and had more advanced disease at baseline compared to the interventional study population. Also, because it was retrospective, there may have been selection bias and missing data. On the other hand, contemporaneous data suggest that diagnostic modalities and disease scoring systems have evolved over time, CALD is now diagnosed earlier through brain MRI screening, often prior to the onset of clinical symptoms. As a result, it is difficult to determine if the observed effects reported in the post-hoc analysis were due to a treatment effect or due to treatment at an early stage of disease with insufficient duration of follow-up to detect progression to MFD or death. In addition to the significant uncertainty about efficacy, 3 cases of MDS mediated by Lenti-D lentiviral vector integration into proto-oncogenes were reported. Given that 1 of the 3 cases of hematological malignancy occurred 7.5 years after administration of gene therapy, long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect as well as side effects.

**Table 7. Study Relevance Limitations**

| Study | Eichler et al. (2024) (26); ALD-102 | NCT03852498 (27); ALD-104 | Skysona prescribing Label (2025) (23) |
|-------|-------------------------------------|---------------------------|---------------------------------------|
|-------|-------------------------------------|---------------------------|---------------------------------------|

|                                          |                                                                                                             |                                                                                                                                         |                                                                                                                                                       |
|------------------------------------------|-------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Population<sup>a</sup></b>            |                                                                                                             | 3. Study population not representative of intended use; potentially included patients with a willing HLA-matched sibling donor for HSCT | 3. Study population not representative of intended use (>90% of study population consisted of parieto-occipital disease)                              |
| <b>Intervention<sup>b</sup></b>          |                                                                                                             |                                                                                                                                         |                                                                                                                                                       |
| <b>Comparator<sup>c</sup></b>            | 5. single arm with no comparator group                                                                      | 5. single arm with no comparator group                                                                                                  | 5. Other (non-contemporaneous historical control, imbalance in known prognostic baseline characteristics that may bias in favor of the treatment arm) |
| <b>Outcomes<sup>d</sup></b>              | 5. Clinically significant difference not prespecified<br>6. Clinically significant difference not supported | 5. Clinically significant difference not prespecified<br>6. Clinically significant difference not supported                             | 5. Clinically significant difference not prespecified<br>6. Clinically significant difference not supported                                           |
| <b>Duration of Follow-up<sup>e</sup></b> |                                                                                                             |                                                                                                                                         | 1. Not sufficient duration for benefit<br>2. Not sufficient duration for harms                                                                        |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

**Table 8. Study Design and Conduct Limitations**

| <b>Study</b>                  | <b>Eichler et al. (2024) (26); ALD-102</b> | <b>NCT03852498 (27); ALD-104</b>       | <b>Skysona prescribing Label (2025) (23)</b> |
|-------------------------------|--------------------------------------------|----------------------------------------|----------------------------------------------|
| <b>Allocation<sup>a</sup></b> | 1. Participants not randomly allocated     | 1. Participants not randomly allocated | 1. Participants not randomly allocated       |

|                                        |                                                                                                                                                                   |                                                                                                                                                                   |                                                                                                                                                                   |
|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                        | 4. Inadequate control for selection bias                                                                                                                          | 4. Inadequate control for selection bias                                                                                                                          | 2. Allocation not concealed<br>3. Allocation concealment unclear<br>4. Inadequate control for selection bias                                                      |
| <b>Blinding<sup>b</sup></b>            | 1. Participants or study staff not blinded<br>2. Outcome assessors not blinded<br>3. Outcome assessed by treating physician<br>4. Outcomes not assessed centrally | 1. Participants or study staff not blinded<br>2. Outcome assessors not blinded<br>3. Outcome assessed by treating physician<br>4. Outcomes not assessed centrally | 1. Participants or study staff not blinded<br>2. Outcome assessors not blinded<br>3. Outcome assessed by treating physician<br>4. Outcomes not assessed centrally |
| <b>Selective Reporting<sup>c</sup></b> |                                                                                                                                                                   | 4. results not published in peer reviewed journal                                                                                                                 | 4. Other (post-hoc subgroup analysis not pre-specified)                                                                                                           |
| <b>Data Completeness<sup>d</sup></b>   |                                                                                                                                                                   |                                                                                                                                                                   |                                                                                                                                                                   |
| <b>Power<sup>e</sup></b>               | 4. Sample size was not determined by formal statistical methods                                                                                                   | 1. Power calculations not reported<br>2. Power not calculated for primary outcome                                                                                 | 1. Power calculations not reported<br>2. Power not calculated for primary outcome<br>3. Power not based on clinically important difference                        |
| <b>Statistical<sup>f</sup></b>         |                                                                                                                                                                   |                                                                                                                                                                   |                                                                                                                                                                   |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

<sup>b</sup> Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

## Section Summary: Cerebral Adrenoleukodystrophy

Evidence consists of an exploratory post-hoc subset analysis of enriched sample comprised of 11 treated individuals compared with 7 untreated individuals who had symptomatic disease at some time during the study (either NFS=1 at baseline or development of symptoms [NFS  $\geq$ 1] during the course of follow-up), and 2 single-arm, open-label studies (ALD-102 and ALD-104). In the post-hoc analysis, the estimated MFD-free survival at month 24 from the time of first NFS  $\geq$ 1 was 72% (95% CI, 35% to 90%) for the symptomatic elivaldogene autotemcel-treated subpopulation and 43% (95% CI, 10% to 73%) for the natural history subpopulations. Notable limitations include post-hoc analysis using a historical control with a limited sample size with known differences in the baseline prognostic variables, such as age at enrollment, age at first NFS  $\geq$ 1, Loes score, and distribution of brain MRI pattern of disease between the 2 groups. As a result, it is difficult to determine whether the observed treatment effect was due to a treatment effect or due to treatment at an early stage of disease with insufficient duration of follow-up to detect progression to MFD or death. In addition to the significant uncertainty about efficacy, 3 cases of myelodysplastic syndrome (MDS) mediated by Lenti-D lentiviral vector integration into proto-oncogenes were reported. Given that 1 of the 3 cases of hematological malignancy occurred 7.5 years after administration of gene therapy, long-term follow-up (>15 years) is required to establish precision around the durability of the treatment effect as well as side effects. In ALD-102, 32 participants with NFS of 0 or 1 and without a willing HLA-matched sibling donor for HSCT received elivaldogene autotemcel. At 24 months, 29 of 32 patients (91%) were alive and free of MFDs. At 48 months, survival free of MFDs was still 91% and the overall survival was 94%. At the most recent follow-up (median, 60.6 months), 26 patients (81%) remained free of MFDs. Furthermore, the NFS remained stable in 30 of 32 patients (94%). The aforementioned case of MDS occurred in this trial. This participant underwent successful allogeneic transplantation at month 95 with no indication of MDS recurrence at month 120. The ALD-104 study, the results of which are currently not published in a peer-reviewed journal, did not stipulate that participants could not have a willing HLA-matched sibling HSC donor for participation. A total of 35 participants received elivaldogene autotemcel. At 24 months, MFD-free survival was achieved in 85.7% of participants. Furthermore, all 35 participants were alive, and 94.3% had a stable NFS.

### Summary of Evidence

For individuals who are assigned male at birth and 4 to 17 years of age with early, active cerebral adrenoleukodystrophy (CALD) who receive elivaldogene autotemcel, the evidence includes a post-hoc analysis from 2 single-arm interventional studies and 2 non-concurrent historical control studies. The results of 1 of the single-arm studies (ALD-102) have been published in a peer-reviewed journal. The interventional studies enrolled patients with early, active CALD as defined by Loes score between 0.5 and 9 (inclusive) and gadolinium enhancement on magnetic resonance imaging (MRI), as well as a neurologic function score (NFS) of  $\leq$ 1, indicating limited changes in neurologic function. The *post-hoc* analysis in an enriched sample of symptomatic study participants compared time from onset of symptoms (NFS  $\geq$ 1) to time to first major functional disability (MFD) or death (i.e., MFD-free survival) in treated (n=11) and natural history untreated (n=7) individuals. Relevant outcomes of interest are overall survival, disease-specific survival, change in disease status, functional outcomes, quality of life, treatment-related morbidity, and treatment-related mortality. The estimated

MFD-free survival at month 24 from time of first NFS  $\geq 1$  was 72% (95% CI, 35% to 90%) for the symptomatic elivaldogene autotemcel-treated subpopulation and 43% (95% CI, 10% to 73%) for the natural history subpopulation. Notable limitations include post-hoc analysis using a historical control with a limited sample size and known differences in the baseline prognostic variables, such as age at enrollment, age at first NFS  $\geq 1$ , Loes score, and distribution of brain MRI pattern of disease between the 2 groups. As a result, it is difficult to determine whether the observed effect was due to a treatment effect or due to treatment at an early stage of disease with insufficient duration of follow-up to detect progression to MFD or death. In addition to the significant uncertainty about efficacy, 3 cases of myelodysplastic syndrome (MDS) mediated by Lenti-D lentiviral vector integration into proto-oncogenes were reported. Given that 1 of the 3 cases of hematological malignancy occurred 7.5 years after administration of gene therapy, long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect as well as side effects. In ALD-102, 32 participants received elivaldogene autotemcel. At month 24, 91% of patients were alive and free of MFDs. At month 48, survival free of MFDs was still 91% and the overall survival was 94%. At the most recent follow-up (median, 60.6 months), 26 patients (81%) remained free of MFDs. Furthermore, NFS remained stable in 30 of 32 patients (94%). The aforementioned case of MDS occurred in this trial. This participant underwent successful allogeneic transplantation at month 95 with no indication of MDS recurrence at month 120. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

## **Practice Guidelines and Position Statements**

### **International Recommendations for the Diagnosis and Management of Patients 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 patient advocacy groups to develop best-practice recommendations for diagnosis, clinical surveillance, and treatment of ALD using a consensus-based modified Delphi approach. (28) 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]  $\leq 9$ ) and a neurological function score of 0 or 1; adult men when they have demyelinating lesions with gadolinium enhancement and no or few neurocognitive impairments.
- 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 policy are listed in Table 9.

**Table 9. Summary of Key Trials**

| NCT Number               | Trial Name                                                                                                                   | Planned Enrollment | Completion Date |
|--------------------------|------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------|
| <b>Ongoing</b>           |                                                                                                                              |                    |                 |
| NCT02698579 <sup>a</sup> | Long-term Follow-up of Participants With Cerebral Adrenoleukodystrophy Who Were Treated With Lenti-D Drug Product            | 64                 | Aug 2038        |
| NCT06224413 <sup>a</sup> | A Study of Participants With Cerebral Adrenoleukodystrophy (CALD) Treated With Elivaldogene Autotemcel                       | 120                | Dec 2047        |
| NCT05939232              | Registry of X-linked Adrenoleukodystrophy                                                                                    | 200                | Dec 2028        |
| <b>Unpublished</b>       |                                                                                                                              |                    |                 |
| NCT03852498 <sup>a</sup> | A Clinical Study to Assess the Efficacy and Safety of Gene Therapy for the Treatment of Cerebral Adrenoleukodystrophy (CALD) | 35                 | May 2024        |

NCT: national clinical trial.

<sup>a</sup> 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.

- 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 5 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.

## Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**



Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

|                    |       |
|--------------------|-------|
| <b>CPT Codes</b>   | None  |
| <b>HCPCS Codes</b> | J3387 |

\*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <<https://www.cms.hhs.gov>>.

| Policy History/Revision |                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Date                    | Description of Change                                                                                                                                                                                                                                                                                                                                                                                                                |
| 01/01/2026              | Document updated. The following change was made to Coverage: Conditional coverage changed to not medically necessary. References 1-28 added; others removed.                                                                                                                                                                                                                                                                         |
| 05/15/2024              | Review only. No changes.                                                                                                                                                                                                                                                                                                                                                                                                             |
| 12/01/2023              | Document updated. The following modification was made to Coverage: Changed from “Individuals aged 17 years or younger...” to “Individuals who are assigned male at birth and 4 to 17 years of age...”. No new references added.                                                                                                                                                                                                      |
| 03/01/2023              | New medical document. Elivaldogene autotemcel (Skysona®) may be considered medically necessary for individuals ages 17 years or younger when the criteria noted in Coverage are met. Repeat treatment of Elivaldogene autotemcel (Skysona®) is considered experimental, investigational, and/or unproven. Elivaldogene autotemcel (Skysona®) is considered experimental, investigational, and/or unproven for all other indications. |